(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 August 2003 (21.08.2003)

PCT

(10) International Publication Number
WO 03/068752 A1

(51) International Patent Classification[7]: C07D 223/16, 409/10, 407/10, 401/10, 413/10, 403/10, 217/04, 209/44, A61K 31/40, 31/47, 31/55, A61P 3/04, 25/30, 25/24, 25/22

(21) International Application Number: PCT/EP03/01545

(22) International Filing Date: 13 February 2003 (13.02.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0203438.7	13 February 2002 (13.02.2002)	GB
0203437.9	13 February 2002 (13.02.2002)	GB
0204784.3	28 February 2002 (28.02.2002)	GB
0204758.7	28 February 2002 (28.02.2002)	GB
0212548.2	30 May 2002 (30.05.2002)	GB
0219711.9	23 August 2002 (23.08.2002)	GB
0224466.3	21 October 2002 (21.10.2002)	GB

(71) Applicant *(for all designated States except US)*: **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 ONN (GB).

(72) Inventors; and

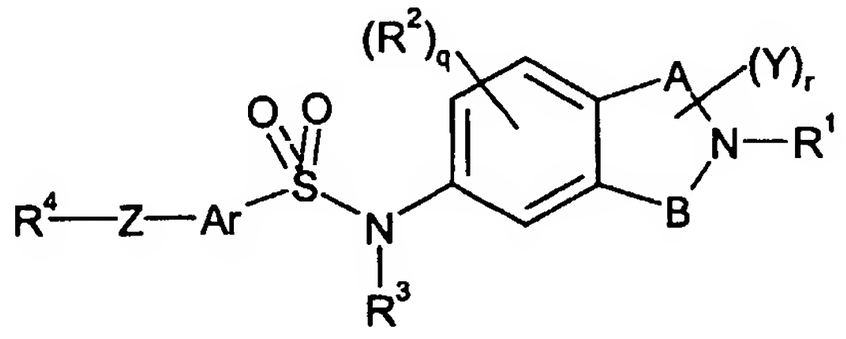
(75) Inventors/Applicants *(for US only)*: **BROMIDGE, Steven, Mark** [GB/IT]; GlaxoSmithKline SpA, Via Alessandro Fleming 2, I-37135 Verona (IT). **COOPER, David, Gwyn** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **FORBES, Ian, Thomson** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **GRIBBLE, Andrew, Derrick** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **JOHNSON, Christopher, Norbert** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **LIGHTFOOT, Andrew, P.** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **MOSS, Stephen, Frederick** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **PAYNE, Andrew, H.** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **RAHMAN, Shahzad, Sharooq** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **WITTY, David, R.** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: **MCKINNELL, Denise**; GlaxoSmithKline, CN925.1, 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,

[Continued on next page]

(54) Title: BENZENESULFONAMIDE DERIVATIVES AS ANTIPSYCHOTIC AGENTS



(I)

(57) Abstract: The invention provides compounds of formula (I)wherein A and B represent the groups -(CH_2)m- and -(CH_2)n-respectively; R^1 represents hydrogen or C_{1-6}alkyl; R^2 represents hydrogen, halogen, hydroxy, cyano, nitro, hydroxyC_{1-6}alkyl, trifluoromethyl, trifluoromethoxy, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{3-7}cycloalkylC_{1-6}alkoxy, -(CH_2)pC_{3-6}cycloalkyl, -(CH_2)pC_{3-6}cycloalkyloxy, -COC_{1-6}alkyl, -SO_2C_{1-6}alkyl, -SOC_{1-6}alkyl, -S-C_{1-6}alkyl, C_{1-6}alkylsulfonyloxy, C_{1-6}alkylsulfonylC_{1-6}alkyl, -CO_2C_{1-6}alkyl, -$CO_2NR^7R^8$, -$SO_2NR^7R^8$, C_{1-6}alkylsulfonamido, C_{1-6}alkylsulfonamidoC_{1-6}alkyl, -(CH_2)$_p$$NR^7R^8$, C_{1-6}alkylamidoC_{1-6}alkyl, -(CH_2)pNR^7COR^8, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6}alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-6}alkyl, arylcarboxamidoC_{1-6}alkyl, aroyl, aroylC_{1-6}alkyl, arylC_{1-6}alkanoyl, -$SO_2NR^7R^8$, optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl, or a group $CONR^7R^8$ or $SO_2NR^7R^8$ wherein R^7 and R^8 together may be fused to form a 5- 7-membered aromatic or non-aromatic heterocyclic ring optionally interrupted by an O or S atom; R^3 represents hydrogen or C_{1-6}alkyl; Ar represents optionally substituted phenyl or optionally substituted monocyclic heteroaryl group; R^4 represents optionally substituted aryl or optionally substituted heteroaryl; R^7 and R^8 each independently represent hydrogen, C_{1-6}alkyl or together form a 5- to 7-membered heterocyclic ring; Z represents a bond, an oxygen atom or C_{1-6}alkyl:Y represents hydrogen or C_{1-6}alkyl; m and n independently represent an integer selected from 1 and 2; p independently represents an integer selected from 0, 1, 2 and 3; q represents an integer from 1 to 3; r represents an integer from 1 to 4; or a pharmaceutically acceptable salt or solvate thereof. The compounds are useful in therapy, in particular as antipsychotic agents.

WO 03/068752 A1

GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) **Designated States** *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

BENZENESULFONAMIDE DERIVATIVES AS ANTIPSYCHOTIC AGENTS

This invention relates to novel compounds, pharmaceutical compositions containing them and their use in therapy, in particular as antipsychotic agents.

WO 98/27081, WO 99/02502, WO 99/37623, WO 99/42465 and WO 01/32646 (SmithKline Beecham plc) disclose a series of aryl sulfonamide and sulfoxide compounds that are said to be 5-HT_6 receptor antagonists and which are claimed to be useful in the treatment of various CNS disorders.

WO 01/62737 discloses amino pyrazole derivatives useful for the treatment of obesity and other disorders associated with the NPY receptor subtype Y5.

EP0937723 discloses sulfonamide compounds useful in the treatment of thrombolytic disorders.

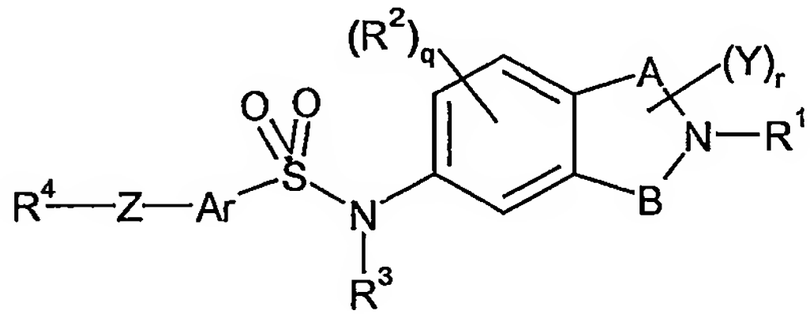
WO 01/85695 discloses tetrahydroisoquinoline analogues useful as growth hormone secretagogues.

US 5,684,195 discloses a method of preparing sulfonamides from sulfones.

WO 02/46164 discloses aryl sulfonamide compounds that are said to be useful as selective ER-β ligands in the treatment or prophylaxis of Alzheimer's disease, anxiety disorders, depressive disorders, osteoporosis, cardiovascular disease, rheumatoid arthritis or prostate cancer.

A structurally novel class of compounds has now been found which are useful as antipsychotic agents and for the treatment of other disorders.

According to the invention, there is provided a compound of formula (I):



(I)

wherein

A and B represent the groups $-(CH_2)_m-$ and $-(CH_2)_n-$respectively;

R^1 represents hydrogen or C_{1-6}alkyl;

R^2 represents hydrogen, halogen, hydroxy, cyano, nitro, hydroxyC_{1-6}alkyl, trifluoromethyl, trifluoromethoxy, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{3-7}cycloalkylC_{1-6}alkoxy, -$(CH_2)_pC_{3-6}$cycloalkyl, -$(CH_2)_pC_{3-6}$cycloalkyloxy, -COC_{1-6}alkyl, -SO_2C_{1-6}alkyl, -SOC_{1-6}alkyl, -S-C_{1-6}alkyl, C_{1-6}alkylsulfonyloxy, C_{1-6}alkylsulfonylC_{1-6}alkyl, -CO_2C_{1-6}alkyl, -$CO_2NR^7R^8$, -$SO_2NR^7R^8$, C_{1-6}alkylsulfonamido, C_{1-6}alkylsulfonamidoC_{1-6}alkyl, -$(CH_2)_pNR^7R^8$, C_{1-6} alkylamidoC_{1-6}alkyl, -$(CH_2)_pNR^7COR^8$, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6}alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-6}alkyl, arylcarboxamidoC_{1-6}alkyl, aroyl, aroylC_{1-6}alkyl, arylC_{1-6}alkanoyl, -$SO_2NR^7R^8$, optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl, or a group $CONR^7R^8$ or $SO_2NR^7R^8$ wherein R^7 and R^8 together may be fused to form a 5- 7-membered aromatic or non-aromatic heterocyclic ring optionally interrupted by an O or S atom;

R^3 represents hydrogen or C_{1-6}alkyl;

Ar represents optionally substituted phenyl or optionally substituted monocyclic heteroaryl group;
R^4 represents optionally substituted aryl or optionally substituted heteroaryl;
R^7 and R^8 each independently represent hydrogen, C_{1-6}alkyl or together form a 5- to 7-membered heterocyclic ring;
Z represents a bond, an oxygen atom or C_{1-6}alkylene:
Y represents hydrogen or C_{1-6}alkyl;
m and n independently represent an integer selected from 1 and 2;
p independently represents an integer selected from 0, 1, 2 and 3;
q represents an integer from 1 to 3;
r represents an integer from 1 to 4;
or a pharmaceutically acceptable salt or solvate thereof.

As a further aspect of the invention, there is provided a compound of formula (I) wherein A, B, Y, Z, q, r, Ar and R^1 to R^4 have any of the meanings as hereinbefore described, with the proviso that when R^1 represents C_{1-6}alkyl and Y represents hydrogen, Ar cannot represent an optionally substituted monocyclic heteroaryl group.

As used herein, the term "alkyl", either alone or as part of another group, refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms. For example, C_{1-6}alkyl means a straight or branched alkyl containing at least 1, and at most 6, carbon atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, isobutyl, isopropyl, t-butyl and 1,1-dimethylpropyl.
As used herein, the term "alkoxy" refers to a straight or branched alkoxy group containing the specified number of carbon atoms. For example, C_{1-6}alkoxy means a straight or branched alkoxy group containing at least 1, and at most 6, carbon atoms. Examples of "alkoxy" as used herein include, but are not limited to, methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy, 2-methylprop-1-oxy, 2-methylprop-2-oxy, pentoxy or hexyloxy.
As used herein, the term "cycloalkyl" refers to a non-aromatic hydrocarbon ring containing the specified number of carbon atoms. For example, C_{3-7}cycloalkyl means a non-aromatic ring containing at least three, and at most seven, ring carbon atoms. Examples of "cycloalkyl" as used herein include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. A C_{6-7}cycloalkyl group is preferred.
As used herein, the term "halogen" refers to the elements fluorine, chlorine, bromine and iodine. Preferred halogens are fluorine, chlorine and bromine.
As used herein, the term "aryl" refers to a phenyl or a naphthyl ring.
As used herein, the term "heteroaryl" refers to a 5- or 6-membered heterocyclic aromatic ring or a fused bicyclic heterocyclic ring system.
As used herein, the term "heterocyclyl" refers to a 3- to 7-membered monocyclic saturated ring containing at least one heteroatom independently selected from oxygen, nitrogen and sulfur. Examples of suitable heterocyclic rings include, but are not limited to, piperidine and morpholine.

As used herein, the term "5- or 6-membered heterocyclic aromatic ring" refers to a monocyclic unsaturated ring containing at least one heteroatom independently selected from oxygen, nitrogen and sulfur. Examples of suitable 5- and 6-membered heterocyclic aromatic rings include, but are not limited to, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, triazinyl, pyridazyl, pyrimidinyl, pyrazolyl, isothiazolyl and isoxazolyl.

As used herein, the term "fused bicyclic heterocyclic ring system" refers to a ring system comprising two 5- to 7-membered saturated or unsaturated rings, the ring system containing at least one heteroatom independently selected from oxygen, nitrogen and sulfur. Preferably, each ring has 5 or 6 ring atoms. Examples of suitable fused bicyclic rings include, but are not limited to, indolyl, indolinyl, benzofuranyl, benzothienyl, quinolyl, isoquinolyl, tetrahydroquinolyl, benzodioxanyl, indanyl and tetrahydronapthyl.

As used herein, the term "optionally substituted" refers to optional substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I) or a salt thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include water, methanol, ethanol and acetic acid. Most preferably the solvent used is water and the solvate may also be referred to as a hydrate.

It will be appreciated that for use in medicine the salts of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include for example acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Other non-pharmaceutically acceptable salts e.g. oxalates, may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention. Also included within the scope of the invention are solvates and hydrates of the compounds of formula (I).

Certain of the compounds of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms thereof.

Certain compounds of formula (I) may exist in stereoisomeric forms (e.g. they may contain one or more asymmetric carbon atoms). The individual stereoisomers (enantiomers and diastereomers) and mixtures of these are included within the scope of the present invention. The present invention also covers the individual isomers of the compounds represented by formula (I) as mixtures with isomers thereof in which one or more chiral centres are inverted. Likewise, it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

The groups R^2, R^5 and R^6 may be located on any free position on their respective phenyl rings. The Y group(s) may be located on any free position on the respective ring.

When R^2, R^4, R^5 or R^6 represent optionally substituted aryl or optionally substituted heteroaryl or R^2 additionally represents optionally substituted heterocyclyl, the optional substituents may be independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro, -NR^7R^8, -C_{1-6}alkylS and –S-C_{1-6}alkyl. More preferably, the optional substituents for the groups R^2, R^4, R^5 and R^6 are independently selected from chloro, fluoro, bromo, methyl, ethyl, t-butyl, methoxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, –S-methyl, –methyl-S and –NR^7R^8.

When Ar represents optionally substituted phenyl or optionally substituted monocyclic heteroaryl, the optional susbtituents are independently selected from hydrogen, halogen, hydroxy, cyano, nitro, hydroxyC_{1-6}alkyl, trifluoromethyl, trifluoromethoxy, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{3-7}cycloalkylC_{1-6}alkoxy, -$(CH_2)_pC_{3-6}$cycloalkyl, -$(CH_2)_pC_{3-6}$cycloalkyloxy, -COC_{1-6}alkyl, -SO_2C_{1-6}alkyl, -SOC_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{1-6}alkylS, C_{1-6}alkylsulfonyloxy, C_{1-6}alkylsulfonylC_{1-6}alkyl, -CO_2C_{1-6}alkyl, -$CO_2NR^7R^8$, -$SO_2NR^7R^8$, C_{1-6}alkylsulfonamido, C_{1-6}alkylsulfonamidoC_{1-6}alkyl, -$(CH_2)_pNR^7R^8$, C_{1-6}alkylamidoC_{1-6}alkyl, -$(CH_2)_pNR^7COR^8$, aryl sulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6}alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-6}alkyl, arylcarboxamidoC_{1-6}alkyl, aroyl, aroylC_{1-6}alkyl, arylC_{1-6}alkanoyl, -$SO_2NR^7R^8$, optionally substituted aryl or optionally substituted heteroaryl, or a group $CONR^7R^8$ or $SO_2NR^7R^8$ wherein R^7 and R^8 together may be fused to form a 5- to 7-membered aromatic or non-aromatic heterocyclic ring optionally interrupted by an O or S atom.

Preferably, R^1 represents hydrogen or C_{1-4}alkyl. More preferably, R^1 represents hydrogen, methyl, ethyl, n-propyl, isopropyl, t-butyl or n-butyl. Even more preferably, R^1 represents hydrogen, methyl, ethyl, n-propyl or isopropyl. Even more preferably, R^1 represents hydrogen or methyl.

Preferably, R^2 represents hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, -C_{1-6}alkylS, –S-C_{1-6}alkyl, -NR^7R^8 or optionally substituted heterocyclyl. In particular, R^2 represents methyl, ethyl, methoxy, ethoxy, isopropoxy, bromo, chloro, dimethylamino, -S-ethyl, -ethyl-S or piperidyl. More preferably, R^2 represents hydrogen, halogen, C_{1-6}alkyl or C_{1-6}alkoxy. Even more preferably, R^2 represents hydrogen, halogen, C_{1-4}alkyl or C_{1-4}alkoxy. Even more preferably, R^2 represents hydrogen, dimethylamino, methoxy, ethoxy or isopropoxy.

Preferably, R^3 represents hydrogen or C_{1-4}alkyl. More preferably, R^3 represents hydrogen, methyl, ethyl, n-propyl or isopropyl. Even more preferably, R^3 represents hydrogen, methyl or isopropyl.

Preferably, R^4 represents phenyl, naphthyl, thienyl, benzofuranyl, furyl, benzothienyl, pyridyl, isoxazolyl and pyrrolyl, all of which may be optionally substituted. More preferably, R^4 represents phenyl, naphthyl, thienyl, benzofuranyl, furyl or benzothienyl, all of which may be optionally substituted. Even more preferably, R^4 represents phenyl or thienyl (e.g. 2-thienyl or 3-thienyl).

If R^4 is optionally substituted, preferably R^4 is mono- or di-substituted. In particular, when R^4 is phenyl, the optional substituents may be independently selected from chloro (e.g. 2-, 3- or 4-chloro), bromo (e.g. 4-bromo), fluoro (e.g. 2-, 3- or 4-fluoro), dichloro (e.g. 2,4- or 3,4-dichloro), difluoro (e.g. 2,4-, 3,4- or 3,5-difluoro), trifluoromethyl (e.g. 4-trifluoromethyl), methyl (e.g. 2-, 3- or 4-methyl), t-butyl (e.g. 4-t-butyl), methoxy (e.g. 4-methoxy),

trifluoromethoxy (e.g. 4-trifluoromethoxy), cyano (e.g. 4-cyano), nitro (e.g. 4-nitro), dimethylamino (e.g. 4-dimethylamino), -methyl-S (e.g. 4-methyl-S), or methyl and chloro together (e.g. 2-methyl-4-chloro or 3-methyl-4-chloro). More preferably, when R^4 is phenyl, one of the optional substituents is located at the 4-position relative to the attachment of R^4 to the rest of the molecule.

When R^4 is thienyl, the optional substituents may be independently selected from chloro (e.g. 5-chloro) or methyl (e.g. 4- or 5-methyl).

Preferably, R^7 and R^8 independently represent hydrogen or C_{1-4}alkyl. More preferably, R^7 and R^8 independently represent hydrogen or methyl.

Preferably, Ar represents optionally substituted phenyl.

Preferably, Z represents a bond or oxygen. More preferably, Z represents a bond.

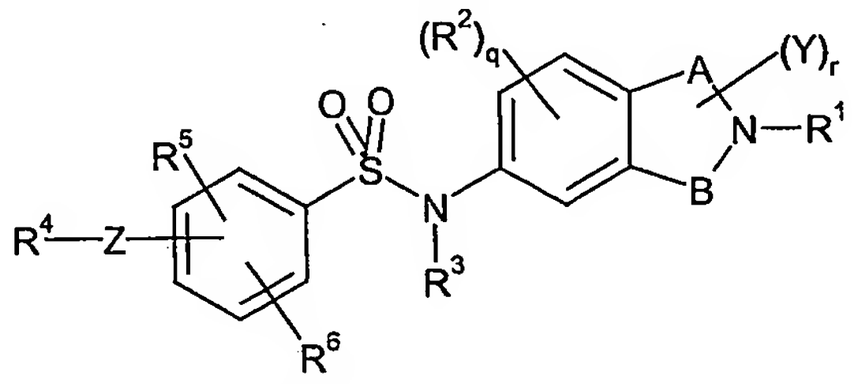
Preferably, Y represents hydrogen.

Preferably, p represents 0.

Preferably, q represents 1.

Preferably, r represents 1.

According to a further aspect of the invention, there is provided a compound of formula (I) wherein Ar represents a phenyl ring, i.e. a compound of formula (IA):

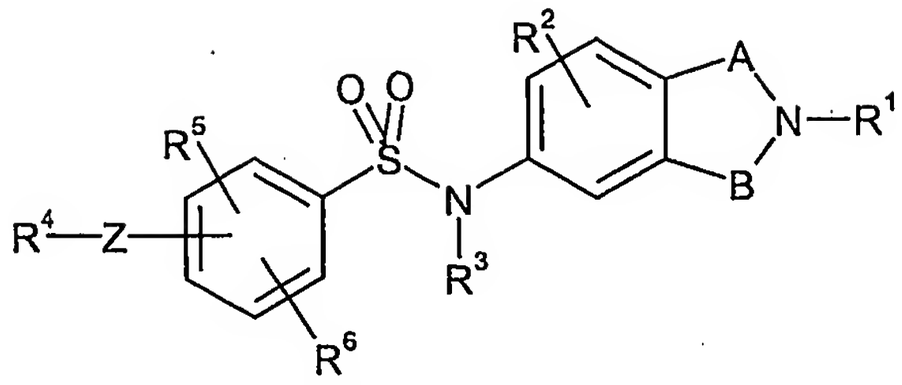


(IA)

or a pharmaceutically acceptable salt or solvate thereof wherein the groups A, B, R^1 to R^4, Z, Y, q and r have any of the meanings as given hereinbefore and R^5 and R^6 each independently represent hydrogen, halogen, hydroxy, cyano, nitro, hydroxyC_{1-6}alkyl, trifluoromethyl, trifluoromethoxy, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{3-7}cycloalkylC_{1-6}alkoxy, -$(CH_2)_pC_{3-6}$cycloalkyl, -$(CH_2)_pC_{3-6}$cycloalkyloxy, -COC_{1-6}alkyl, -SO_2C_{1-6}alkyl, -SOC_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{1-6}alkylS, C_{1-6}alkylsulfonyloxy, C_{1-6}alkylsulfonylC_{1-6}alkyl, -CO_2C_{1-6}alkyl, -$CO_2NR^7R^8$, -$SO_2NR^7R^8$, C_{1-6}alkylsulfonamido, C_{1-6}alkylsulfonamidoC_{1-6}alkyl, -$(CH_2)_pNR^7R^8$, C_{1-6}alkylamidoC_{1-6}alkyl, -$(CH_2)_pNR^7COR^8$, aryl sulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6}alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-6}alkyl, arylcarboxamidoC_{1-6}alkyl, aroyl, aroylC_{1-6}alkyl, arylC_{1-6}alkanoyl, -$SO_2NR^7R^8$, optionally substituted aryl or optionally substituted heteroaryl, or a group $CONR^7R^8$ or $SO_2NR^7R^8$ wherein R^7 and R^8 together may be fused to form a 5- to 7-membered aromatic or non-aromatic heterocyclic ring optionally interrupted by an O or S atom.

Preferably, R^5 and R^6 independently represent hydrogen, methyl, fluoro or chloro.

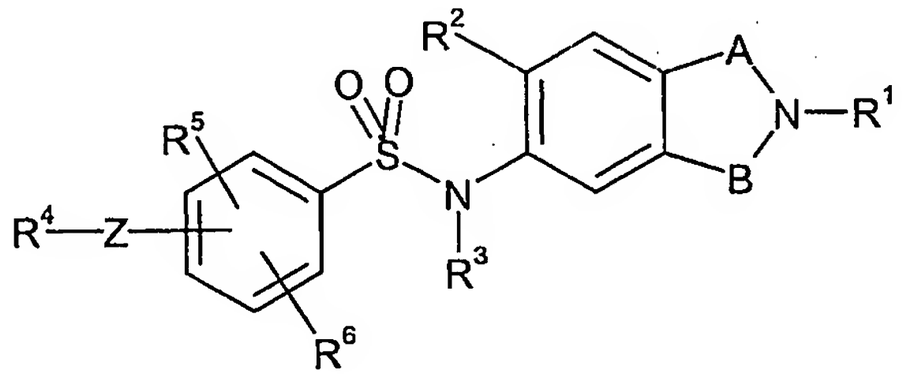
According to a further aspect of the invention, there is provided a compound of formula (IA) wherein q represents 1, r represents 1 and Y represents hydrogen, i.e. a compound of the formula (IB):



(IB)

or a pharmaceutically acceptable salt or solvate thereof wherein the groups A, B, R^1 to R^6 and Z have any of the meanings as given hereinbefore.

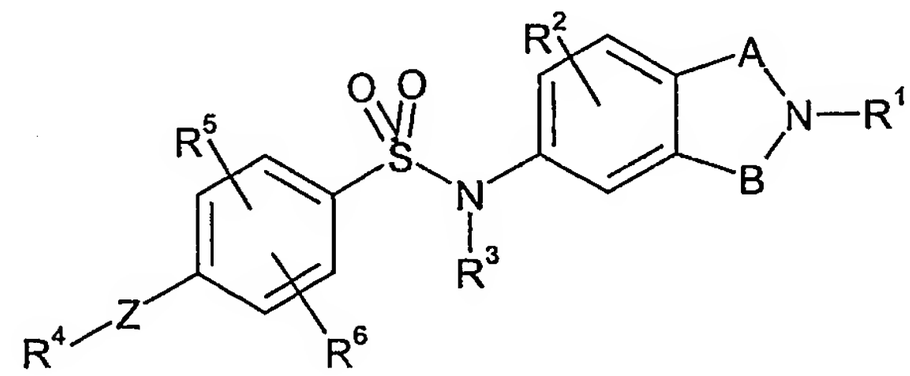
According to a further aspect of the invention, there is provided a compound of formula (IB) wherein the R^2 group is located at the para-position relative to the group B, i.e. a compound of formula (IC):



(IC)

or a pharmaceutically acceptable salt or solvate thereof wherein the groups A, B, R^1 to R^6 and Z have any of the meanings as given hereinbefore.

According to a further aspect of the invention, there is provided a compound of formula (IB) wherein the group $-Z-R^4$ is located at the para-position relative to the sulfonamide group, i.e. a compound of formula (ID)



(ID)

wherein

A and B represent the groups $-(CH_2)_m-$ and $-(CH_2)_n-$respectively;

R^1 represents hydrogen or C_{1-6}alkyl;

R^2 represents hydrogen, halogen, hydroxy, cyano, nitro, hydroxyC_{1-6}alkyl, trifluoromethyl, trifluoromethoxy, C_{1-6}alkyl, C_{1-6}alkoxy, $-(CH_2)_pC_{3-6}$cycloalkyl, $-(CH_2)_pC_{3-6}$cycloalkyloxy, $-COC_{1-6}$alkyl, $-SO_2C_{1-6}$alkyl, $-SOC_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-CO_2C_{1-6}$alkyl, $-CO_2NR^7R^8$, $-SO_2NR^7R^8$, $-(CH_2)_pNR^7R^8$, $-(CH_2)_pNR^7COR^8$, optionally substituted aryl, optionally substituted heteroaryl, a fused bicyclic heterocyclic ring system or optionally substituted heterocyclyl;

R^3 represents hydrogen or C_{1-6}alkyl;

R^4 represents optionally substituted aryl or optionally substituted heteroaryl;

R^5 and R^6 each independently represent hydrogen, halogen, hydroxy, cyano, nitro, hydroxyC_{1-6}alkyl, trifluoromethyl, trifluoromethoxy, C_{1-6}alkyl, C_{1-6}alkoxy, -$(CH_2)_pC_{3-6}$cycloalkyl, -$(CH_2)_pC_{3-6}$cycloalkyloxy, -COC_{1-6}alkyl, -SO_2C_{1-6}alkyl, -SOC_{1-6}alkyl, -S-C_{1-6}alkyl, -CO_2C_{1-6}alkyl, -$CO_2NR^7R^8$, -$SO_2NR^7R^8$, -$(CH_2)_pNR^7R^8$, -$(CH_2)_pNR^7COR^8$, optionally substituted aryl, optionally substituted heteroaryl or a fused bicyclic heterocyclic ring system;

R^7 and R^8 each independently represent hydrogen or C_{1-6}alkyl;

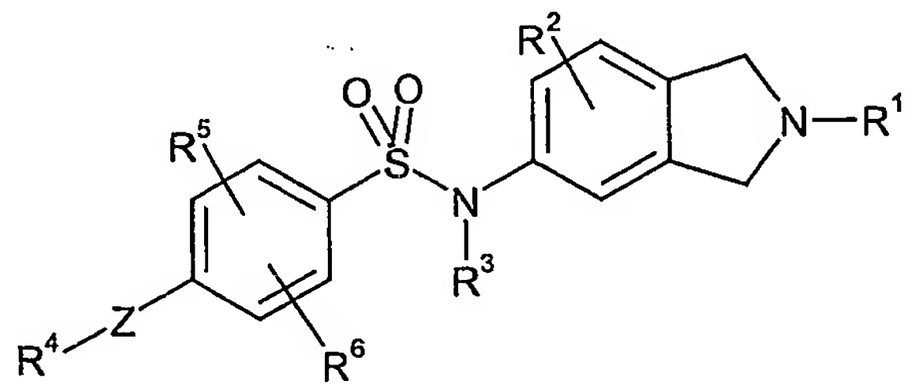
Z represents a bond, an oxygen atom or C_{1-6}alkylene;

m and n independently represent an integer selected from 1 and 2;

p independently represents an integer selected from 0, 1, 2 and 3;

or a pharmaceutically acceptable salt or solvate thereof.

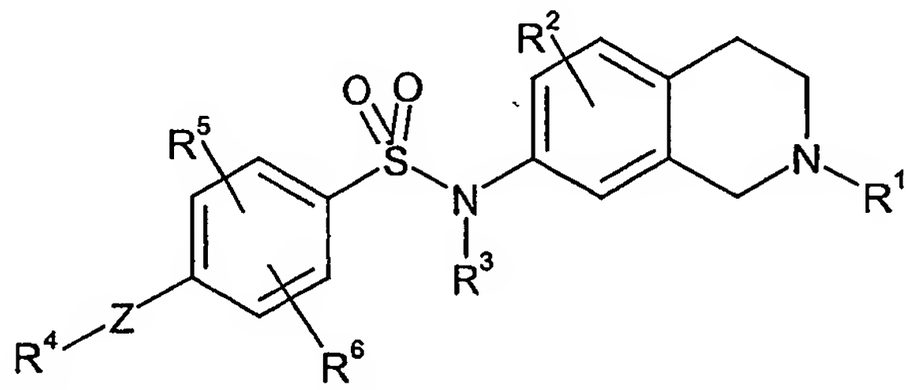
According to a further aspect of the invention, there is provided a compound of formula (ID) wherein m is 1 and n is 1, i.e. a compound of formula (IE):



(IE)

or a pharmaceutically acceptable salt or solvate thereof wherein the groups Z and R^1 to R^6 have any of the meanings as given hereinbefore.

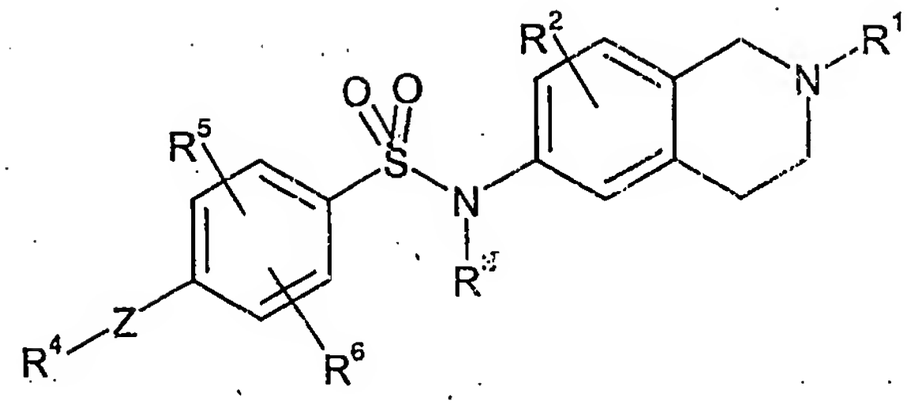
According to a further aspect of the invention, there is provided a compound of formula (ID) wherein m is 2 and n is 1, i.e. a compound of formula (IF):



(IF)

or a pharmaceutically acceptable salt or solvate thereof wherein the groups Z and R^1 to R^6 have any of the meanings as given hereinbefore.

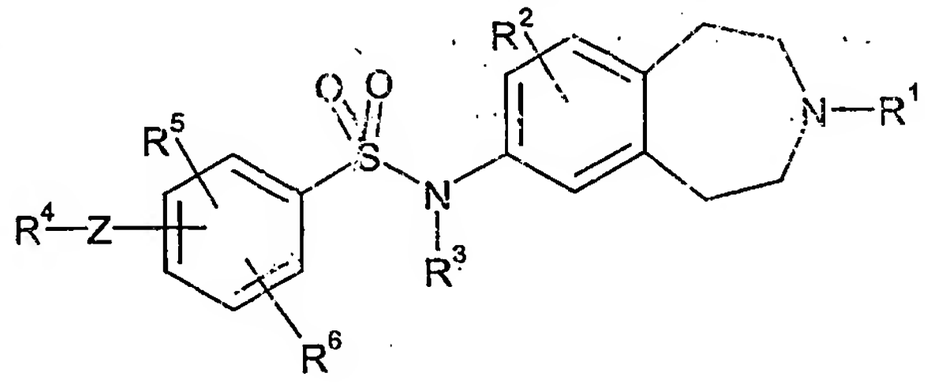
According to a further aspect of the invention, there is provided a compound of formula (ID) wherein m is 1 and n is 2, i.e. a compound of formula (IG):



(IG)

or a pharmaceutically acceptable salt or solvate thereof wherein the groups Z and R^1 to R^6 have any of the meanings as given hereinbefore.

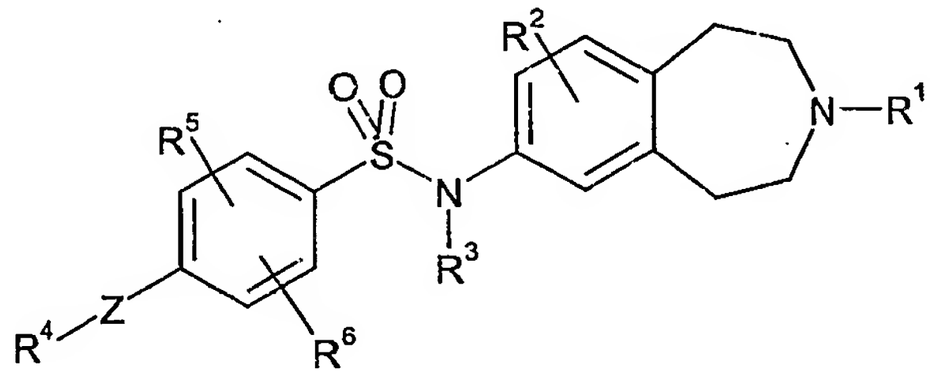
According to a further aspect of the invention, there is provided a compound of formula (IB) wherein m is 2 and n is 2, i.e. a compound of formula (IH):



(IH)

or a pharmaceutically acceptable salt or solvate thereof wherein the groups Z and R^1 to R^6 have any of the meanings as given hereinbefore.

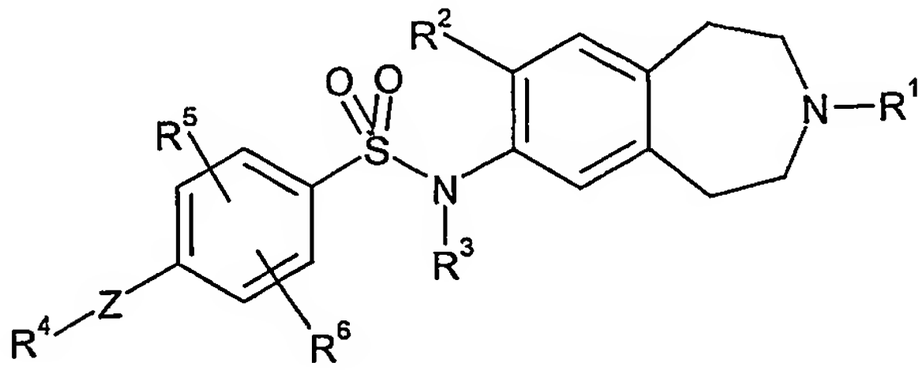
According to a further aspect of the invention, there is provided a compound of formula (ID) wherein m is 2 and n is 2, i.e. a compound of formula (IJ):



(IJ)

or a pharmaceutically acceptable salt or solvate thereof wherein the groups Z and R^1 to R^6 have any of the meanings as given hereinbefore.

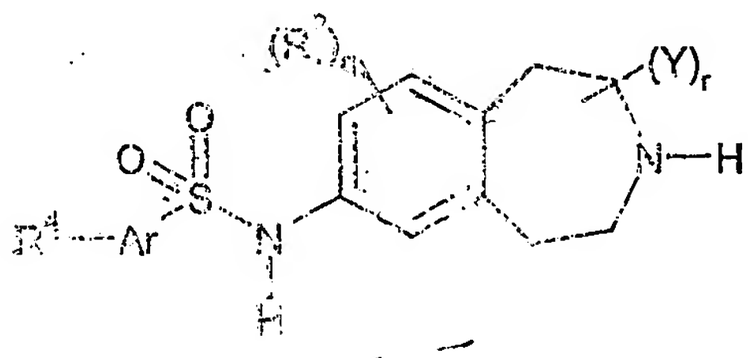
According to a further aspect of the invention, there is provided a compound of formula (IJ) wherein the R^2 group is located at the para-position relative to the group B, i.e. a compound of formula (IK):



(IK)

or a pharmaceutically acceptable salt or solvate thereof wherein the groups Z and R^1 to R^6 have any of the meanings as given hereinbefore.

According to a further aspect of the invention, there is provided a compound of formula (I) wherein R^1 and R^3 both represent hydrogen, m and n both represent 2 and Z represents a bond, i.e. a compound of formula (IL):



(IL)

wherein:

R^2 represents hydrogen, halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, C_{1-5} alkyl, trifluoromethanesulfonyloxy, pentafluoroethyl, C_{1-6} alkoxy, arylC$_{1-6}$ alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6} alkyl, C_{1-6} alkylsulfonamido, C_{1-6} alkylamido, C_{1-5} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-6} alkyl, arylcarboxamidoC_{1-6} alkyl, aroyl, aroylC_{1-6} alkyl, arylC_{1-6} alkanoyl, or a group $CONR^7R^8$ or $SO_2NR^7R^8$, wherein R^7 and R^8 independently represent hydrogen or C_{1-5} alkyl or together may be fused to form a 5- to 7- membered aromatic or non-aromatic heterocyclic ring optionally interrupted by an O or S atom;

Y represents hydrogen or C_{1-6} alkyl;

q represents an integer from 1 to 3;

r represents an integer from 1 to 4;

Ar and R^4 independently represent phenyl or a monocyclic heteroaryl group each of which may be optionally substituted;

Ar and R^4 may be optionally substituted by one or more substituents which may be the same or different, and which are selected from those defined for R^2;

or solvates thereof.

According to a further aspect of the invention, there is provided a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof wherein the groups A, B, R^1 to R^4, Y, q and r have any of the meanings as given hereinbefore and Z represents oxygen or C_{1-6} alkylene.

According to a further aspect of the invention, there is provided a compound of formula (IA) or a pharmaceutically acceptable salt or solvate thereof wherein the groups A, B, R^1 to R^4, Y, q and r have any of the meanings as given hereinbefore and Z represents oxygen or C_{1-6} alkylene.

According to a further aspect of the invention, there is provided a compound of formula (IB) or a pharmaceutically acceptable salt or solvate thereof wherein the groups A, B and R^1 to R^6 have any of the meanings as given hereinbefore and Z represents oxygen or C_{1-6} alkylene.

According to a further aspect of the invention, there is provided a compound of formula (IC) or a pharmaceutically acceptable salt or solvate thereof wherein the groups A, B and R^1 to R^6 have any of the meanings as given hereinbefore and Z represents oxygen or C_{1-6}alkylene.

According to a further aspect of the invention, there is provided a compound of formula (ID) or a pharmaceutically acceptable salt or solvate thereof wherein the groups A, B and R^1 to R^6 have any of the meanings as given hereinbefore and Z represents oxygen or C_{1-6}alkylene.

According to a further aspect of the invention, there is provided a compound of formula (IE) or a pharmaceutically acceptable salt or solvate thereof wherein the groups R^1 to R^6 have any of the meanings as given hereinbefore and Z represents oxygen or C_{1-6}alkylene.

According to a further aspect of the invention, there is provided a compound of formula (IF) or a pharmaceutically acceptable salt or solvate thereof wherein the groups R^1 to R^6 have any of the meanings as given hereinbefore and Z represents oxygen or C_{1-6}alkylene.

According to a further aspect of the invention, there is provided a compound of formula (IG) or a pharmaceutically acceptable salt or solvate thereof wherein the groups R^1 to R^6 have any of the meanings as given hereinbefore and Z represents oxygen or C_{1-6}alkylene.

According to a further aspect of the invention, there is provided a compound of formula (IH) or a pharmaceutically acceptable salt or solvate thereof wherein the groups R^1 to R^6 have any of the meanings as given hereinbefore and Z represents oxygen or C_{1-6}alkylene.

According to a further aspect of the invention, there is provided a compound of formula (IJ) or a pharmaceutically acceptable salt or solvate thereof wherein the groups R^1 to R^6 have any of the meanings as given hereinbefore and Z represents oxygen or C_{1-6}alkylene.

According to a further aspect of the invention, there is provided a compound of formula (IK) or a pharmaceutically acceptable salt or solvate thereof wherein the groups R^1 to R^6 have any of the meanings as given hereinbefore and Z represents oxygen or C_{1-6}alkylene.

According to a further aspect of the invention, there is provided a compound of formula (IL) or a pharmaceutically acceptable salt or solvate thereof wherein the groups R^1 to R^6 have any of the meanings as given hereinbefore and Z represents oxygen or C_{1-6}alkylene.

In a preferred aspect of the invention, compounds of formula (I) are of the formulae (IE), (IF), (IH), (IJ) and (IK) or a pharmaceutically acceptable salt or solvate thereof wherein the groups Z and R^1 to R^6 have any of the meanings as given hereinbefore.

Particular compounds according to the invention include those incorporated in Tables 1 to 3 and those specifically exemplified and named hereinafter including, without limitation:-

4-(4-Chloro-phenyl)-*N*-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide;

4-(4-Chloro-phenyl)-*N*-(3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide;

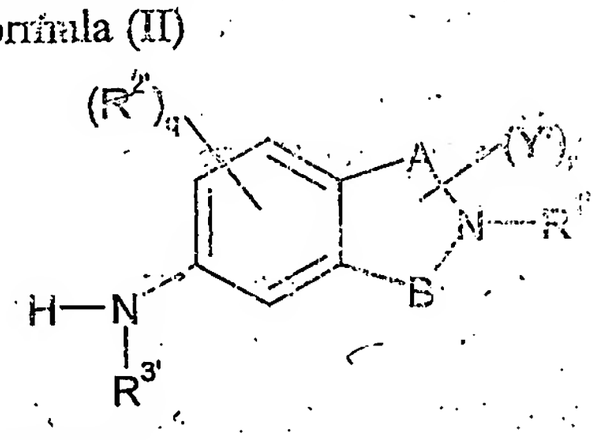
4-(4-Chloro-phenyl)-*N*-methyl-*N*-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide;

4-(4-Chloro-phenyl)-*N*-methyl-*N*-(3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide;

4-(3,4-Dichloro-phenyl)-*N*-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide hydrochloride;

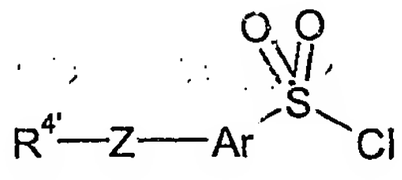
4-(4-Chloro-phenyl)-*N*-(8-methoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide hydrochloride;
4-(4-Chloro-phenyl)-*N*-(8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide hydrochloride;
4-(4-Chloro-phenyl)-*N*-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-benzenesulfonamide;
4-(4-Chloro-phenyl)-*N*-(2,3-dihydro-1*H*-isoindol-5-yl)-benzenesulfonamide hydrochloride;
4-(4-Chloro-phenyl)-*N*-(2-methyl-2,3-dihydro-1*H*-isoindol-5-yl)-benzenesulfonamide;
4-(4-Chloro-phenyl)-3-methyl-*N*-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide hydrochloride;
4-(4-Chloro-phenyl)-3-methyl-*N*-(3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide;
4-(4-Chloro-phenyl)-3-methyl-*N*-(8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide hydrochloride;
4-(4-Chloro-phenyl)-3-methyl-*N*-(8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide;
4-(5-Chloro-thiophen-2-yl)-N-(8-methoxy-3-methyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-benzenesulfonamide;
4-(5-Chloro-thiophen-2-yl)-2-fluoro-N-(8-methoxy-3-methyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-benzenesulfonamide;
4-(4-Chloro-phenyl)-*N*-(8-dimethylamino-3-methyl-2,3,4,5-tetrahydro-1*H*-benzazepin-7-yl)-benzenesulfonamide hydrochloride and
4-(4-fluorobenzyl)-*N*-(3-methyl-2,3,4,5-tetrahydro-1*H*-benzo[d]azepin-7-yl)-benzenesulfonamide hydrochloride.

The compounds of the present invention may be in the form of their free base or pharmaceutically acceptable salts thereof, particularly the monohydrochloride salt.
The present invention also provides a general process (A) for preparing compounds of formula (I) which process comprises:
reacting a compound of formula (II)



(II)

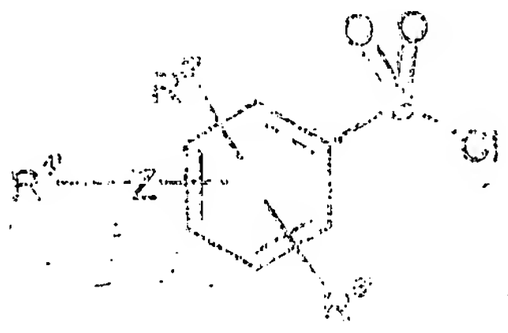
with a compound of formula (III)



(III)

wherein A, B, Z, q and r are as hereinbefore defined and $R^{1'}$-$R^{4'}$ and Y' represent R^1 to R^4 and Y as hereinbefore defined or are groups that may be readily convertible to R^1 to R^4.
This general method (A) can be conveniently performed by mixing the two components in a suitable solvent such as pyridine or dichloromethane (in the presence of a base), at 0°C.

According to a further aspect of the invention, when compounds of the formula (II) are prepared by method (A), a compound of formula (II) as hereinbefore defined is reacted with a compound of formula (IIIa)

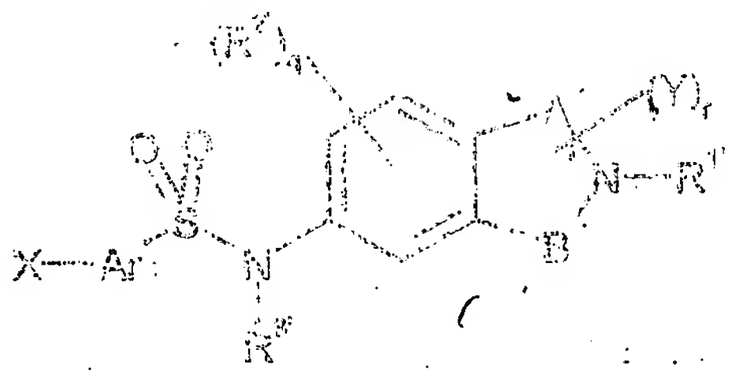


(IIIa)

wherein A, B, Z, q and r are as hereinbefore defined and $R^{1'}$-$R^{6'}$ and Y' represent R^1 to R^6 and Y as hereinbefore defined or are groups that may be readily convertible to R^1 to R^6.

The present invention also provides a general process (B) for preparing compounds of formula (I) wherein Z is a bond, which process comprises:

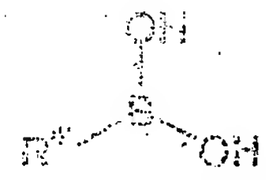
reacting a compound of formula (IV)



(IV)

wherein X is a leaving group, such as iodo, bromo or triflate, and A, B, q, r and Y are as hereinbefore defined and $R^{1'}$-$R^{3'}$ represent R^1 to R^3 as hereinbefore defined or are groups that may be readily convertible to R^1 to R^3,

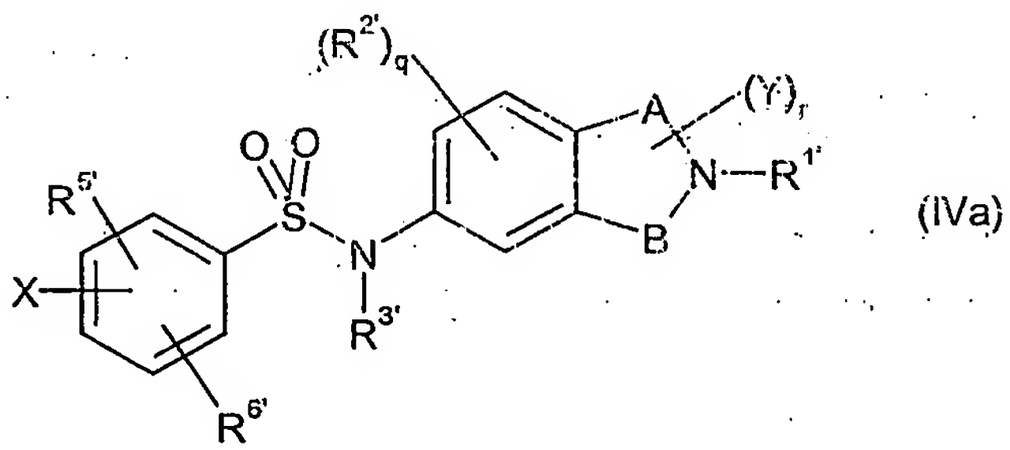
with an aryl boronic acid of formula (V)



(V)

wherein $R^{4'}$ represents R^4 as hereinbefore defined or is a group that may be readily convertible to R^4, under standard Suzuki conditions, e.g. treatment of compound (IV) with 4-chlorobenzeneboronic acid in toluene containing aqueous sodium carbonate and a catalytic amount of $Pd(PPh_3)_4$, at reflux under argon.

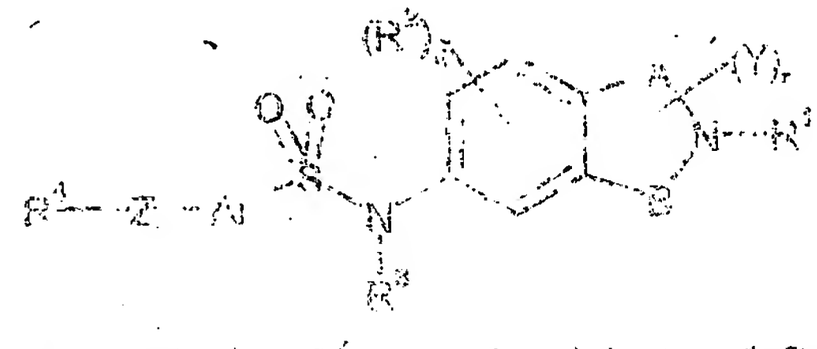
According to a further aspect of the invention, when compounds of the formula (II) are prepared by method (B), a compound of formula (IVa)



(IVa)

wherein X is a leaving group, such as iodo, bromo or triflate, and A, B, q, r and Y are as hereinbefore defined and R^1'-R^6' represent R^1 to R^6 as hereinbefore defined or are groups that may be readily convertible to R^1 to R^6,
with an aryl boronic acid of formula (V) as hereinbefore defined.

The present invention also provides a general process (C) for preparing compounds of formula (I) which process comprises:
converting a compound of formula (I)



(I)

wherein A, B, Z, Y, q, r and R^1 to R^6 are as hereinbefore defined, into another compound of formula (I) by substituting the group R^1 or the group R^2 using conventional techniques.
Interconversion of one of the R^1 to R^6 groups to the corresponding R^1 to R^6 groups typically arises when one compound of formula (I) is used as the immediate precursor of another compound of formula (I), or when it is easier to introduce a more complex or reactive substituent at the end of a synthetic sequence.
For example, conversion of R^1 from a t-butoxycarbonyl (BOC) group to hydrogen is conducted by the treatment of the N-BOC protected compound with hydrogen chloride in ethanol or dioxan at room temperature.
Conversion of R^1 from hydrogen to an alkyl group is conducted by the treatment of the NH compound with the appropriate aldehyde in dichloroethane in the presence of a reducing agent, such as sodium triacetoxyborohydride, or by the treatment of the NH compound with the appropriate alkyl halide, such as iodomethane, under standard alkylation conditions (potassium carbonate in DMF at 60°C).
Conversion of R^3 from hydrogen to an alkyl group is conducted by the treatment of the sulfonamide NH compound with the appropriate alcohol, such as methanol, under Mitsunobu conditions, for example treatment with diisopropyl azodicarboxylate/triphenylphosphine and methanol in tetrahydrofuran at room temperature.
Compounds of formula (II) are known in the literature or may be prepared by known processes, for example, reduction of the corresponding nitro compound as disclosed in WO 99/14197, or by procedures analogous to these procedures. Suitable examples of an R^1' protecting group are trifluoroacetyl or the t-butoxycarbonyl (BOC) group.
Compounds of formula (III) are commercially available or may be prepared by established procedures, for example chlorosulfonylation of a suitable substituted aromatic precursor, using chlorosulfonic acid, for example as described in J. Med. Chem., 2000, 43, 156-166.
Compounds of formula (IV) may be prepared from compounds of formula (II) by the treatment with the appropriate 4-substituted benzenesulfonyl chloride using standard conditions, for example in pyridine or dichloromethane in the presence of a base such as triethylamine at room temperature.

Compounds of formula (V) are commercially available or may be prepared by known methodology for example lithiation of a suitable substituted bromobenzene at low temperature followed by quenching with tri-isopropylborate and acidic hydrolysis of the reaction product

Compounds of formula (I) have been found to exhibit affinity for dopamine receptors, in particular the D_3 and D_2 receptors, and are useful in the treatment of disease states which require modulation of such receptors, such as psychotic conditions. Many of the compounds of formula (I) have also been found to have greater affinity for dopamine D_3 than for D_2 receptors. The therapeutic effect of currently available antipsychotic agents (neuroleptics) is generally believed to be exerted via blockade of D_2 receptors; however this mechanism is also thought to be responsible for undesirable extrapyramidal side effects (eps) associated with many neuroleptic agents. Without wishing to be bound by theory, it has been suggested that blockade of the dopamine D_3 receptor may give rise to beneficial antipsychotic activity without significant eps. (see for example Sokoloff et al, Nature, 1990; 347: 146-151; and Schwartz et al, Clinical Neuropharmacology, Vol 16, No. 4, 295-314, 1993). Additionally, certain compounds of formula (I) have antagonist affinity for the serotonin 5-HT_{2A}, 5-HT_{2C} and 5-HT_6 receptors. These additional properties may give rise to enhanced anti-psychotic activity (e.g. improved effects on cognitive dysfunction) and/or reduced eps. These could include, but are not limited to, attenuation of cognitive symptoms via 5-HT_6 receptor blockade (see Reavill, C. and Rogers, D.C., 2001, Investigational Drugs 2, 104-109), and reduced anxiety (see for example Kennett et al., Neuropharmacology 1997 Apr-May; 36 (4-5); 609-20), protection against eps (Reavill et al. Brit. J. Pharmacol., 1999; 126: 572-574) and antidepressant activity (Bristow et al., Neuropharmacology 39:2000; 1222-1236) via 5-HT_{1B} receptor blockade.

Compounds of formula (I) may also exhibit affinity for other receptors not mentioned above, resulting in beneficial antipsychotic activity

The compounds of formula (I) are of use as antipsychotic agents for example in the treatment of schizophrenia, schizo-affective disorders, schizophreniform diseases, psychotic depression, mania, acute mania, paranoid and delusional disorders. Furthermore, they may have utility as adjunct therapy in Parkinson Disease, particularly with compounds such as L-DOPA and possibly dopaminergic agonists, to reduce the side effects experienced with these treatments on long term use (e.g. see Schwartz et al., Brain Res. Reviews, 1998, 26, 236-242). From the localisation of D_3 receptors, it could also be envisaged that the compounds could also have utility for the treatment of substance abuse where it has been suggested that D_3 receptors are involved (e.g. see Levant, 1997, Pharmacol. Rev., 49, 231-252). Examples of such substance abuse include alcohol, cocaine, heroin and nicotine abuse. Other conditions which may be treated by the compounds include dyskinetic disorders such as Parkinson's disease, neuroleptic-induced parkinsonism and tardive dyskinesias; depression; anxiety; agitation; tension; social or emotional withdrawal in psychotic patients; cognitive impairment including memory disorders such as Alzheimer's disease; psychotic states associated with neurodegenerative disorders, e.g. Alzheimer's disease; eating disorders; obesity; sexual dysfunction; sleep disorders; emesis; movement disorders; obsessive-compulsive disorders; amnesia; aggression; autism; vertigo; dementia; circadian rhythm disorders; and gastric

motility disorders e.g. IBS. Therefore, the invention provides a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt or solvate thereof for use in therapy.

The invention also provides a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in a condition which requires modulation of a dopamine receptor.

The invention also provides a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt or solvate thereof for use in the treatment of psychotic disorders, Parkinsons disease, substance abuse, dyskinetic disorders, depression, bipolar disorder, anxiety, cognitive impairment, eating disorders, obesity, sexual dysfunction, sleep disorders, emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, autism, vertigo, dementia, circadian rhythm disorders and gastric motility disorders.

The invention also provides the use of a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment of a condition which requires modulation of a dopamine receptor.

The invention also provides the use of a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment of psychotic disorders, Parkinsons disease, substance abuse, dyskinetic disorders, depression, bipolar disorder, anxiety, cognitive impairment, eating disorders, obesity, sexual dysfunction, sleep disorders, emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, autism, vertigo, dementia, circadian rhythm disorders and gastric motility disorders.

The invention also provides a method of treating a condition which requires modulation of a dopamine receptor, which comprises administering to a mammal in need thereof an effective amount of a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt or solvate thereof.

In a further aspect, the invention provides a method of treating psychotic disorders, Parkinsons disease, substance abuse, dyskinetic disorders, depression, bipolar disorder, anxiety, cognitive impairment, eating disorders, obesity, sexual dysfunction, sleep disorders, emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, autism, vertigo, dementia, circadian rhythm disorders and gastric motility disorders which comprises administering to a mammal in need thereof an effective amount of a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt or solvate thereof.

A preferred use for dopamine antagonists according to the present invention is in the treatment of psychotic disorders, Parkinsons disease, substance abuse, dyskinetic disorders, depression, bipolar disorder, anxiety and cognitive impairment.

"Treatment" includes prophylaxis, where this is appropriate for the relevant condition(s).

For use in medicine, the compounds of the present invention are usually administered as a standard pharmaceutical composition. The present invention therefore provides in a further aspect a pharmaceutical composition comprising a compound of formula (I) as hereinbefore described or a pharmaceutically (i.e. physiologically) acceptable salt thereof and a pharmaceutically (i.e. physiologically) acceptable carrier. The pharmaceutical composition can be for use in the treatment of any of the conditions described herein.

The compounds of formula (I) may be administered by any convenient method, for example by oral, parenteral (e.g. intravenous), buccal, sublingual, nasal, rectal or transdermal administration and the pharmaceutical compositions adapted accordingly.

The compounds of formula (I) as hereinbefore described and their pharmaceutically acceptable salts which are active when given orally can be formulated as liquids or solids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a pharmaceutically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as a fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomiser.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

Compositions suitable for transdermal administration include ointments, gels and patches.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The pharmaceutically acceptable compounds of the invention will normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose of between 1 mg and 500 mg, preferably between 10 mg and 400 mg, e.g. between 10 and 250 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 50 mg, e.g. between 1 and 25 mg of the compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

Biological Test Methods

Binding experiments on cloned dopamine (e.g. D_2 and D_3) receptors

The ability of the compounds to bind selectively to human D_2/D_3 dopamine receptors can be demonstrated by measuring their binding to cloned receptors. The inhibition constants (K_i) of test compounds for displacement of [^{125}I]-Iodosulpride binding to human D_2/D_3 receptors expressed in CHO cells were determined as follows. The cell lines were shown to be free from bacterial, fungal and mycoplasmal contaminants, and stocks of each were stored frozen in liquid nitrogen. Cultures were grown as monolayers or in suspension in standard cell culture media. Cells were recovered by scraping (from monolayers) or by centrifugation (from suspension cultures), and were washed two or three times by suspension in phosphate buffered saline followed by collection by centrifugation. Cell pellets were stored frozen at -80°C. Crude cell membranes were prepared by homogenisation followed by high-speed centrifugation, and characterisation of cloned receptors achieved by radioligand binding.

Preparation of CHO cell membranes: Cell pellets were gently thawed at room temperature and resuspended in about 20 volumes of ice-cold extraction buffer, 5mM EGTA, 50mM Trizma pre-set crystals (pH7.4@37°C), 1mM $MgCl_2$, 5mM KCl and 120mM NaCl. The suspension was homogenised using an Ultra-Turrax at full speed for 15 seconds. The homogenate was centrifuged at 18,000 r.p.m for 15 min at 4°C in a Sorvall RC5C centrifuge. Supernatant was discarded and homogenate re-suspended in extraction buffer then centrifugation was repeated. The final pellet was resuspended in 50mM Trizma pre-set crystals (pH 7.4 @ 37°C) and stored in 1ml aliquot tubes at -80°C (D2 = 3.0E+08 cells, D3 = 7.0E+07 cells and D4 = 1.0E+08 cells). The protein content was determined using a BCA protocol and bovine serum albumin as a standard (Smith, P. K., et al., Measurement of protein using bicinchoninic acid, Anal. Biochem. 150, 76-85 (1985)).

Binding experiments:

Binding experiments on D_2/D_3 receptors

Crude D_2/D_3 cell membranes were incubated with 0.03nM [^{125}I]-Iodosulpride (~2000 Ci/mmol; Amersham, U. K., and the test compound in a buffer containing 50mM Trizma pre-set crystals (pH 7.4 @ 37°C), 120mM NaCl, 5mM KCl, 2mM $CaCl_2$, 1mM $MgCl_2$, 0.3% (w/v) bovine serum albumin. The total volume is 0.2ml and incubated in a water bath at 37°C for 40 minutes. Following incubation, samples were filtered onto GF/B Unifilters using a

Canberra Packard Filtermate, and washed four times with ice-cold 50mM Trizma pre-set crystals (pH 7.4 @ 17°C). The radioactivity on the filters was measured using a Canberra Packard Top-Count Scintillation counter. Non-specific binding was defined with 10μM SKF-102101 (YM-09151). For competition curves, 10 serial log concentrations of competing cold drug were used (Dilution range: 10μM-10pM). Competition curves were analysed using Inflexion, an iterative curve fitting programme in Excel. Results were expressed as pK_i values where

$pK_i = -\log10[Ki]$.

The exemplified compounds have pK_i values within the range of 6.6 – 9.6 at the dopamine D_3 receptor.

The exemplified compounds have pK_i values within the range of 5.3 –9.3 at the dopamine D_2 receptor.

Binding experiments on cloned 5-HT_6 receptors

Compounds were tested following the procedures outlined in WO 98/27081. All of the exemplified compounds have pK_i values within the range of 7.0 – 8.8 at the serotonin 5-HT_6 receptor.

Binding experiments on cloned 5-HT_{2C} receptors

Compounds were tested following the procedures outlined in WO 94/04533. All of the exemplified compounds have pK_i values within the range of 6.6 – 8.4 at the serotonin 5-HT_{2C} receptor.

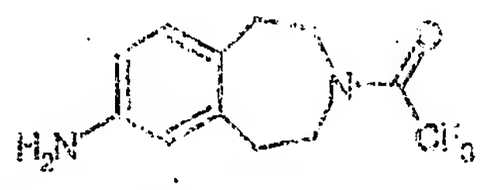
Binding experiments on cloned 5-HT_{1A} receptors

Compounds can be tested following the procedures outlined in *British Journal of Pharmacology* (1996) 117, 427-434. All of the exemplified compounds have pKi values within the range of 6.3 – 8.9 at the serotonin 5-HT_{1A} receptor

The invention is further illustrated by the following non-limiting examples:

Description 1

1-(7-Amino-1,2,4,5-tetrahydro-3-benzazepin-3-yl)-2,2,2-trifluoro-ethanone (D1)



7-Nitro-1,2,4,5-tetrahydro-3*H*-3-benzazepine (D1a)

1,2,4,5-Tetrahydro-3*H*-benzazepine (1 g) (See P. Ruggli et al., Helv. Chim. Acta, 18, 1388, [1935]) was added slowly dropwise to stirred fuming nitric acid (25 ml) at -10°C. Stirring was continued at -10°C for 1 hour and the reaction mixture was then poured onto ice, the precipitate collected by filtration and dried to give the title compound as the nitrate salt, 1.4g. This salt was suspended in water, cooled to 5°C and neutralised with 5M sodium hydroxide. The precipitate was collected by filtration, recrystallised from water and dried, affording the title compound D1a as a white solid (0.6 g).

1-(7-Nitro-1,2,4,5-tetrahydro-3-benzazepin-3-yl)-2,2,2-trifluoro-ethanone (D1b)

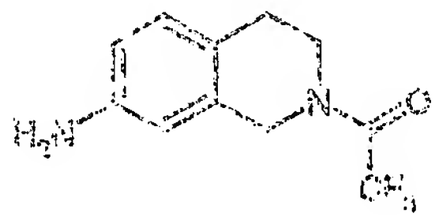
The 7-nitro benzazepine derivative (5 g) was dissolved in dichloromethane (80 ml) and to this was added diisopropylethylamine (5.4 ml) in dichloromethane (20 ml) at 0°C, followed by a solution of trifluoroacetic anhydride (4.3 ml) in dichloromethane (20 ml) at 0°C. The mixture was allowed to warm to room temperature and stirred overnight. Aqueous work up with water and dichloromethane gave the title compound D1b (7.9 g). MH^+ 289

1-(7-Amino-1,2,4,5-tetrahydro-3-benzazepin-3-yl)-2,2,2-trifluoro-ethanone (D1)

The nitro derivative D1b was hydrogenated in accordance with the procedure described in D2c to give the title compound D1. MH^+ 259

Description 2

7-Amino-1,2,3,4-tetrahydro-2-trifluoroacetyl-isoquinoline (D2)



N-2-(4-Nitrophenyl)ethyl-trifluoroacetamide (D2a)

A solution of trifluoroacetic anhydride (10.6ml) in dichloromethane (100ml) was added dropwise to a stirred solution of 2,6-lutidine (17.44ml) and 4-nitrophenethylamine hydrochloride (15.2g; 75 mmol) at 0°C. The mixture was stirred at 25°C overnight under argon and then washed with dilute citric acid (2 x), brine and dried over Na_2SO_4. The material in the organic phase gave the title compound D2a as a pale yellow solid (19.04g).

7-Nitro-1,2,3,4-tetrahydro-2-trifluoroacetyl-isoquinoline (D2b)

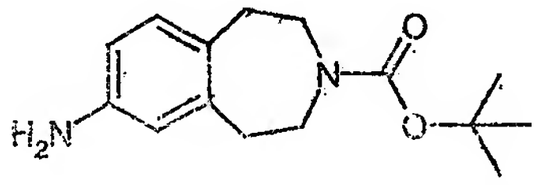
The nitro compound D2a (2.26g; 9.15 mmol) and paraformaldehyde (0.45g; 14.6 mmol) in acetic acid (30ml) and conc. H_2SO_4 (15ml) were stirred at 25°C for 24h according to the procedure of G.E. Stokker., Tet. Let., 1996, 37, 5453. Work up afforded the title compound D2b as a white solid (2.17g). ^1H NMR ($CDCl_3$) δ: 3.10 (2H, m), 3.92 (2H, m), 4.83 + 4.92 (2H, 2xs), 7.38 (1H, t), 8.10 (2H, m). $m/_Z$ (EI): 274 (M^+).

7-Amino-1,2,3,4-tetrahydro-2-trifluoroacetyl-isoquinoline (D2)

The 7-nitro compound D2b (0.99g, 3.6 mmol) in ethanol (50 ml) was hydrogenated over 10% palladium on carbon (450 mg) at atmospheric pressure for 4 h. The catalyst was removed by filtration through a pad of celite and evaporation gave the title compound D2 as a colourless solid (840mg). ^{1}H NMR ($CDCl_3$) δ: 2.84 (2H, t), 3.23 (2H, bs), 3.82 (2H, m), 4.66 (2H, d), 6.47 (1H, m), 6.57 (1H, m), 6.96 (1H, m).

Description 3

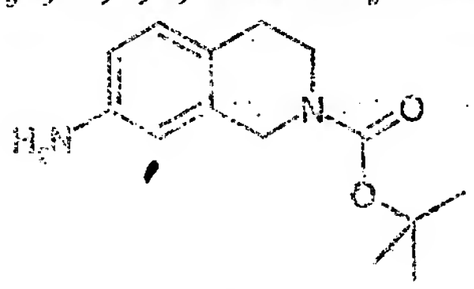
7-Amino-1,2,4,5-tetrahydro-3-benzazepine-3-carboxylic acid *tert*-butyl ester (D3)



The title compound D3 was prepared using a similar methodology to that described in EP 284384. MH^+ 263

Description 4

7-Amino-2-(*t*-butyloxycarbonyl)-1,2,3,4-tetrahydroisoquinoline (D4)



7-Nitro-1,2,3,4-tetrahydroisoquinoline (D4a)

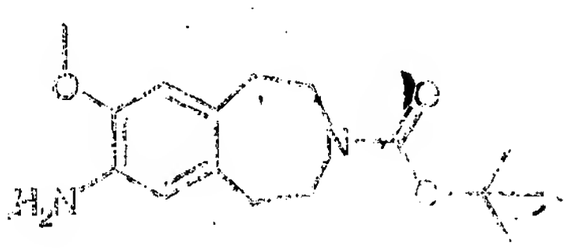
The trifluoroacetamide D2b (17.22g; 63 mmol) was hydrolysed at room temperature using a solution of potassium carbonate (46.6g) in 10% aqueous methanol (660ml). Work-up with dichloromethane gave the title compound D4a (11g).

7-Amino-2-(*t*-butyloxycarbonyl)-1,2,3,4-tetrahydroisoquinoline (D4)

The title compound D4 was prepared from the compound D4a using di-*t*-butyl dicarbonate in 10% aqueous hydroxide in dioxan at 25°C followed by catalytic hydrogenation according to the procedure described for D2a. MH^+ 249.

Description 5

7-Amino-8-methoxy-1,2,4,5-tetrahydro-3-benzazepine-3-carboxylic acid *tert*-butyl ester (D5)



7-Methoxy-1,2,4,5-tetrahydro-3-benzazepine-3-carboxylic acid tert-butyl ester (D5a)

To a solution of 7-hydroxy-1,2,4,5-tetrahydro-3-benzazepine-3-carboxylic acid *tert*-butyl ester (5 g, 19 mmol) in dimethylformamide (50ml) was added potassium carbonate (3.4 g, 25 mmol) and methyl iodide (3.25 ml, 60 mmol). The mixture was heated to 30°C for 12h. The

solvent was evaporated and the residue partitioned between dichloromethane (100 ml) and water (100 ml). The organic layer was separated and evaporated to give the crude product D5a as a colourless oil (5.3 g, 100%).

7-Methoxy-8-nitro-1,2,4,5-tetrahydro-3-benzazepine-3-carboxylic acid *tert*-butyl ester (D5b)

To a mixture of 7-methoxy-1,2,4,5-tetrahydro-3-benzazepine-3-carboxylic acid *tert*-butyl ester (D5a) (5.3 g, 19 mmol) in glacial acetic acid (100 ml) and acetic anhydride (10 ml) at 0°C was added a mixture of nitric acid (70% aqueous, 5 g, 55 mmol) dropwise in glacial acetic acid (100 ml) and acetic anhydride (10 ml) maintaining the temperature below 5°C. The mixture was stirred at room temperature for 2 h and then poured into ice/water (500 ml). The aqueous was extracted with dichloromethane (2 x 200 ml) and the combined organic portions were neutralised with saturated sodium bicarbonate solution. The dichloromethane layer was evaporated and the residue chromatographed on silica gel (eluent: hexane/dichloromethane (1:1) to dichloromethane) to give the product D5b as a colourless solid (1.5 g, 25%).

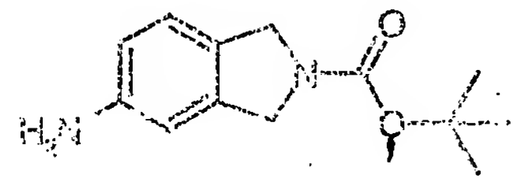
7-Amino-8-methoxy-1,2,4,5-tetrahydro-3-benzazepine-3-carboxylic acid *tert*-butyl ester (D5)

To a solution of 7-methoxy-8-nitro-1,2,4,5-tetrahydro-3-benzazepine-3-carboxylic acid *tert*-butyl ester D2b (1.5 g, 4.7 mmol) in ethanol (80 ml) was added palladium on charcoal (10%, 0.5 g). The mixture was stirred under an atmosphere of hydrogen for 2 h and then filtered. The solvent was evaporated to give the title compound D5 as a colourless solid (1.35 g, 100%).

Mass spectrum AP$^+$: Found 193 ([M-Boc]$^+$). $C_{16}H_{24}N_2O_3$ requires 292. ^{1}H NMR ($CDCl_3$) δ 1.48 (9H, s), 2.76 (4H, m), 3.51 (4H, m), 3.65 (2H, s), 3.82 (3H, s), 6.50 (1H, m), 6.56 (1H; m).

Description 6.

5-Amino-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester (D6)



5-Nitroisoindoline nitrate (D6a)

Isoindoline (4g, 33.1mmol) was added to 95% sulphuric acid, the reaction was treated carefully with fuming nitric acid (2.2ml) at 0°C and stirred for 1 h, then the mixture was poured onto ice and the resulting precipitate was collected by filtration and dried *in vacuo* to afford the title compound D6a (4.1g, 40%); ^{1}H NMR (DMSO-d^6) 8.35 (1H, s), 8.35 (1H, d, 8.4Hz), 7.70 (1H, d, 8.4Hz), 4.61 (4H,s).

5-Nitro-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester (D6b)

The compound D6a (3.0g, 13.47mmol) in dichloromethane (50ml) was treated with triethylamine (4.09g, 40.42mmol) followed by di-tert-butyl dicarbonate (3.09g, 14.15mmol) and stirred at room temperature for 3 days. The reaction was then diluted with dichloromethane and washed with 3N citric acid, sodium bicarbonate solution, water and

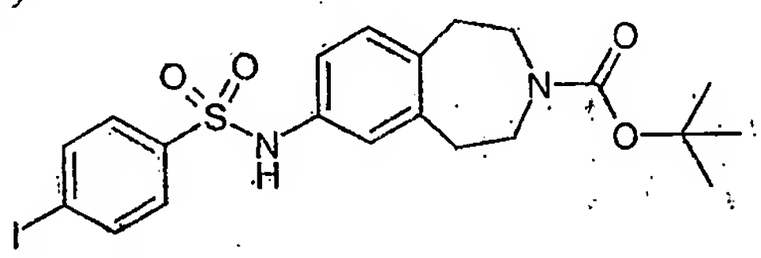
brine. The organic phase was separated, dried over anhydrous sodium sulfate and evaporated *in vacuo* to afford the title compound D6b (3.5g, 98%); ^{1}H NMR ($CDCl_3$) 8.19 (2H, m), 7.26 (1H, m), 4.75 (4H, m), 1.52 (9H, s).

5-Amino-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester (D6)

The compound D6b (3.5g, 13.25mmol) was dissolved in ethanol (200ml) and treated with 10 wt% Palladium on charcoal (1g), and stirred under 1 atm of H_2 for 16 hours. The reaction was filtered and evaporated *in vacuo* to afford the title compound D6 (3.01g, 96%); MS (ES+), m/e 235 $[MH]^+$. ^{1}H NMR: δ $CDCl_3$ 1.52 (9H, s), 4.74 (2H, s), 4.77 (2H, s), 7.4 (1H, m), 8.2 (2H, m).

Description 7

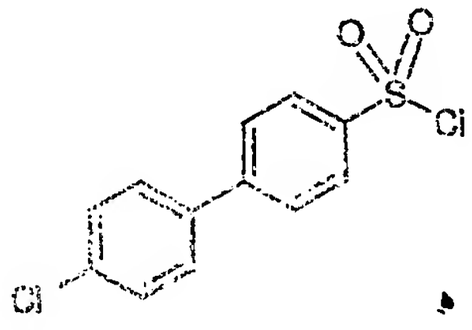
7-(4-Iodo-benzenesulfonylamino)-1,2,4,5-tetrahydro-3-benzazepine-3-carboxylic acid *tert*-butyl ester (D7)



To a solution of D3 (4.7 g, 18 mmol) in pyridine (40 ml) at 0°C was added dropwise a solution of 4-iodophenylsulfonyl chloride (6.1 g, 20 mmol) in dichloromethane (20 ml). The reaction mixture was then stirred at room temperature for 18 h, then poured onto brine. This mixture was extracted with ethyl acetate (3 x), and the combined organic layers washed with citric acid solution, sodium bicarbonate solution then brine. The organic layer was dried over sodium sulfate then evaporated to afford the crude product. Chromatography on silica, eluting with 20-50% ethyl acetate/hexane afforded the title compound D7 (8 g). MH^+ 529

Description 8

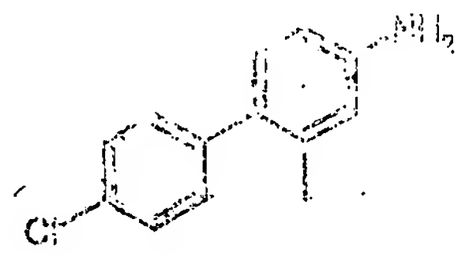
4'-Chloro-biphenyl-4-sulfonyl chloride (D8)



The title compound D8 was prepared from 4-chlorobiphenyl by chlorosulfonation with chlorosulfonic acid using the classical procedure (J. Med. Chem., 2000, 43, 156-166).

Description 9

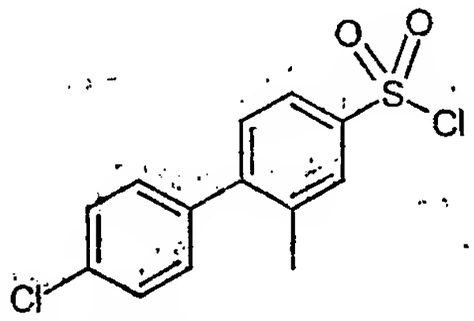
4'-Chloro-2-methyl-biphenyl-4-ylamine hydrochloride (D9)



A mixture of 4-chlorophenyl boronic acid (6.32 g), 3-methyl-4-bromoaniline (5 g), toluene (135 ml), ethanol (40 ml) and potassium carbonate solution (40 ml) was degassed and then stirred under an atmosphere of argon. Tetrakis(triphenylphosphine)palladium(0) (0.62 g) was added and the mixture was stirred at reflux for 18 hours. The mixture was treated with water and ethyl acetate, then the organic layer was separated, washed with brine and evaporated. The residue was chromatographed on silica eluted with 10% ethyl acetate in hexane, and treated with hydrogen chloride in ether to give the title compound D9 as a white solid. ^{1}H NMR: δ DMSO-d^6 2.23 (3H, s); 7.2 (3H, m), 7.4 (2H, d); 7.5 (2H, d)

Description 10

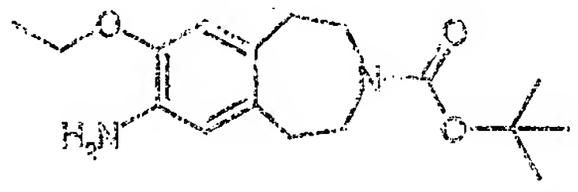
4'-Chloro-2-methyl-biphenyl-4-sulfonyl chloride (D10)



A stirred suspension of 4'-chloro-2-methyl-biphenyl-4-ylamine hydrochloride D9 (2.76 g) was cooled to –5°C and treated with a solution of sodium nitrite (1.2 g) in water (10 ml). The resulting solution was stirred for 30 minutes, treated with urea (0.3 g) then added to a suspension of cuprous chloride (1 g) in acetic acid (30 ml) which had been saturated with sulfur dioxide stirred at 5°C. The solution was allowed to warm to room temperature over 1 hour, then heated to 40°C for 30 minutes. Extraction with dichloromethane and chromatography on silica eluted with 5% ethyl acetate in hexane gave the title compound D10 as a white solid (1.65 g) ^{1}H NMR: δ $CDCl_3$ 2.37 (3H, s), 7.2 (2H, m), 7.4 (3H, m), 7.9 (2H, m).

Description 11

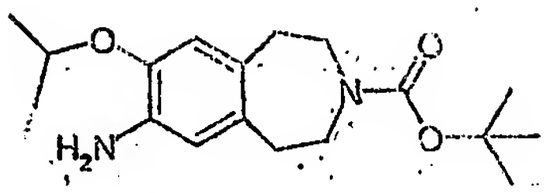
7-Amino-8-ethoxy-1,2,4,5-tetrahydro-3-benzazepine-3-carboxylic acid *tert*-butyl ester (D11)



The title compound D11 was prepared in accordance with Description 5, but methyl iodide was replaced with ethyl iodide for the alkylation of the phenol ^{1}H NMR ($CDCl_3$) δ 6.55 (1H, s), 6.51 (1H, s), 4.05 (2H, q, J = 7.0 Hz), 3.68 (2H, s), 3.51 (4H, m), 2.75 (4H, m), 1.48 (9H, s), 1.41 (3H, t, J = 7.0 Hz).

Description 12

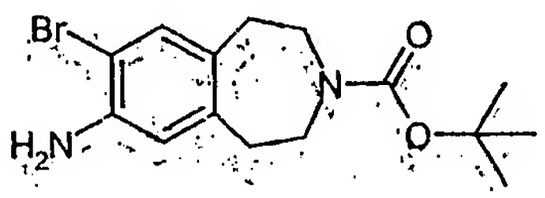
7-Amino-8-isopropoxy-1,2,4,5-tetrahydro-3-benzazepine-3-carboxylic acid *tert*-butyl ester (D12)



The title compound was prepared in accordance with Description 5, but methyl iodide was replaced with isopropyl iodide for the alkylation of the phenol. ^{1}H NMR ($CDCl_3$) δ 6.57 (1H, s), 6.50 (1H, s), 4.46 (1H, sept, J = 6.1 Hz), 3.68 (2H, s), 3.51 (4H, m), 2.74 (4H, m), 1.48 (9H, s), 1.33 (6H, d, J = 6.1 Hz).

Description 13

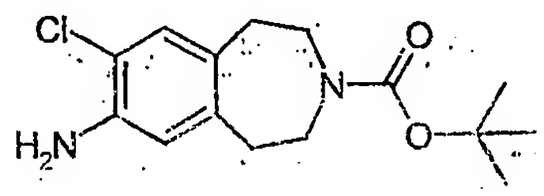
7-Amino-8-bromo-1,2,4,5-tetrahydro-3-benzazepine-3-carboxylic acid *tert*-butyl ester (D13)



The aniline D3 (5 g, 19 mmol) was dissolved in dry acetonitrile (100 ml) and the solution was cooled to -15 °C. A solution of N-bromosuccinimide (1.03 eq, 19.6 mmol, 3.48 g, in 70 ml of dry acetonitrile) was added dropwise at -15 °C to the solution containing the aniline over 20 min. After the addition, the reaction mixture was left to warm up to room temperature for 10 min and then it was poured onto water/brine (150 ml + 15 ml). The aqueous was extracted with EtOAc (100 ml, 50 ml), the organics were combined, dried over Na_2SO_4, filtered and the solvent was evaporated to afford the crude product. Chromatography on silica eluting with 5-30% EtOAc/n-hexane afforded the title compound D13 (1.3 g). $(M^+ - Boc) = 241$.

Description 14

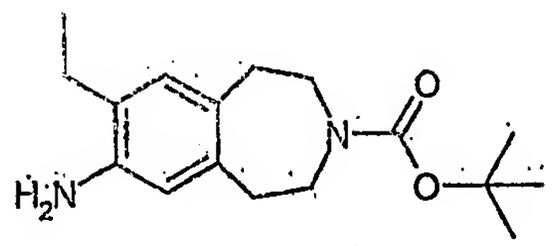
7-Amino-8-chloro-1,2,4,5-tetrahydro-3-benzazepine-3-carboxylic acid *tert*-butyl ester (D14)



To a stirred solution of D3 (10 g, 38 mmol) in acetonitrile (300 ml) at 0 °C was added N-chlorosuccinimide (6.6 g, 49 mmol) portionwise over 10 minutes. The resulting solution was stirred overnight at room temperature, then water (500 ml) and EtOAc (500 ml) were added. The organic layer was separated, dried over magnesium sulfate and concentrated *in vacuo* to give a dark brown oil. This oil was purified by column chromatography using 20% diethyl ether/hexane as the eluant to give the title compound D14 as an orange glassy solid. (MH-Boc)$^+$ 197.1, 199.1

Description 15

7-Amino-8-ethyl-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester (D15)



7-Hydroxy-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester (D15a)

The title compound was prepared according to the procedure described in WO 00/21951 i.e. 7-Methoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine (10 g) in 48% aqueous hydrobromic acid (350 ml) was allowed to stir at 100°C for 4 h. The mixture was allowed to cool to 20°C then evaporated to dryness; giving the crude hydroxy compound as a brown solid (14.5 g). This solid was dissolved in tetrahydrofuran (100 ml) and water (70 ml) and triethylamine (8 g) was added dropwise; followed by a solution of di-*tert*-butyl dicarbonate (14 g) in tetrahydrofuran (20 ml). The resulting mixture was allowed to stir at 20°C for 16 h then partitioned between ethyl acetate (200 ml) and water (200 ml). The aqueous layer was extracted with ethyl acetate (100 ml). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (100 ml), dried over anhydrous sodium sulfate and evaporated to dryness. The resulting oil was purified by chromatography over silica gel, eluting with 10-30% ethyl acetate in hexane, affording the title compound D15a as a white solid (8 g), MS (APT): Found 164 (MH^+-Boc). $C_{15}H_{21}NO_3$ requires 263. ^1H NMR: δ $CDCl_3$ 1.48 (9H, s), 2.75-2.87 (4H, m), 3.40-3.60 (4H, m), 4.95 (1H; s), 6.50-6.62 (2H, m), 6.96 (1H, d).

7-Hydroxy-8-nitro-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester (D15b)

Nitration of D15a was carried out by adding 70% aqueous nitric acid (8 g) dissolved in glacial acetic acid (100 ml)/acetic anhydride (10 ml) to the phenol D15a (20 g) dissolved in AcOH (200 ml)/acetic anhydride (20 ml) at 0°C. Aqueous work-up followed by chromatography on silica gel using 0-20% EtOAc/n-hexane as eluant afforded the title compound D15b (11 g). ^1H NMR ($CDCl_3$) δ 7.85 (1H; s), 6.93 (1H; s), 3.56 (4H, m), 2.91 (4H; m), 1.48 (9H; m).

7-Nitro-8-trifluoromethanesulfonyloxy-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester (D15c)

D15b (8.4 g) was dissolved in acetone (300 ml) and cooled to 0°C. Trifluoromethanesulfonyl chloride (4.4 ml) was added and the resultant mixture stirred at room temperature for 2h. Evaporation in vacuo followed by basic aqueous work-up afforded the title compound D15c (12 g). ^1H NMR ($CDCl_3$) δ 7.95 (1H, s), 7.19 (1H, s), 3.61 (4H, m), 3.02 (4H, m), 1.48 (9H, m).

7-Nitro-8-vinyl-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester (D15d)

A mixture of D15c (500 mg), vinyl tri-n-butyltin (0.4 ml), lithium chloride (145 mg), palladium tetrakistriphenylphosphine (131 mg) and 2,6-di-*tert*-butylphenol (4 mg) in 1,4-dioxan (4 ml) was heated at 160°C for 0.5h in a sealed tube in a Smith microwave reactor. Aqueous work-up followed by chromatography using 0-20% EtOAc/n-hexane as eluent gave the title compound D15d (260 mg).

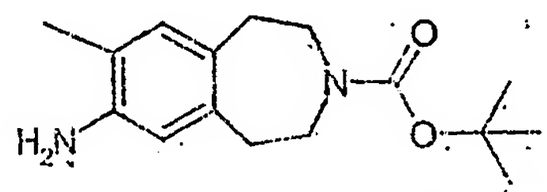
7-Amino-8-ethyl-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester (D15)

Hydrogenation of D15d (260 mg) at 50psi in ethanol (40 ml) over 10% palladium on charcoal (100 mg, paste) at room temperature afforded the title compound D15 (190 mg).

MH^+ 291

Description 16

7-Amino-8-methyl-1,2,4,5-tetrahydro-3-benzazepine-3-carboxylic acid *tert*-butyl ester (D16)



7-Methyl-8-nitro-1,2,4,5-tetrahydro[d]azepine-3-carboxylic acid *tert*-butyl ester (D16a)

A mixture of D15c (1.0 g), tetramethyltin (0.6 ml), lithium chloride (0.29 g), palladium tetrakistriphenylphosphine (0.13 g) and 2,6-di-*tert*-butylphenol (cat.) in 1,4-dioxan (4 ml) was heated at 160°C for 0.5h in a sealed tube in a Smith microwave reactor. Aqueous work-up followed by chromatography using 0-20% EtOAc/n-hexane as eluent gave the title compound D16a (0.44 g).

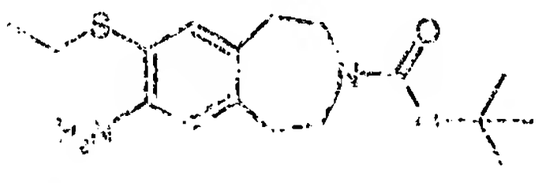
7-Amino-8-methyl-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester (D16)

Hydrogenation of D16a (440 mg) at 50psi in ethanol (100 ml) over 10% palladium on charcoal (200 mg, paste) at room temperature afforded the title compound D16 (330 mg).

$(MH\text{-}Boc)^+$ 177.

Description 17

7-Amino-8-ethylsulfanyl-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester (D17)



7-Nitro-8-ethylsulfanyl-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester (D17a)

A suspension of BINAP (100 mg), palladium(II) acetate (70 mg) and caesium carbonate (956 mg) in dioxan (5 ml) was sonicated for 30 min at room temperature. To the resulting red mixture was added D15c (0.5 g) and ethane thiol (0.2 ml) and the mixture was heated in a

Smith microwave reactor for 30 mins at 160°C. The mixture was diluted with diethyl ether (30 ml) and water (30 ml) and the layers were separated. The aqueous portion was extracted with a further portion of diethyl ether (10 ml) and the combined organic extracts were washed with saturated sodium bicarbonate solution and then dried (Na_2SO_4), filtered and evaporated. Chromatography using 0-10% EtOAc/n-hexane as eluent gave the title compound D17a (0.23 g).

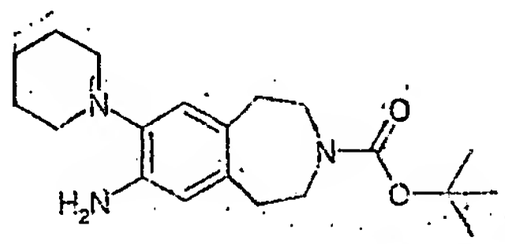
7-Amino-8-ethylsulfanyl-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester (D17)

Hydrogenation of D17a (0.23 g) at 50psi in ethanol (50 ml) over 10% palladium on charcoal (200 mg, paste) at room temperature afforded the title compound D17 (192 mg).

^{1}H NMR ($CDCl_3$) δ 7.12 (1H; s); 6.52 (1H; s), 4.23 (2H; m), 3.51 (4H; m), 2.72 (6H; m); 1.48 (9H; m); 1.22 (3H, t; J = 7.4 Hz).

Description 18

7-Amino-8-piperidin-1-yl-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester (D18)



7-Nitro-8- piperidin-1-yl-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester (D18a)

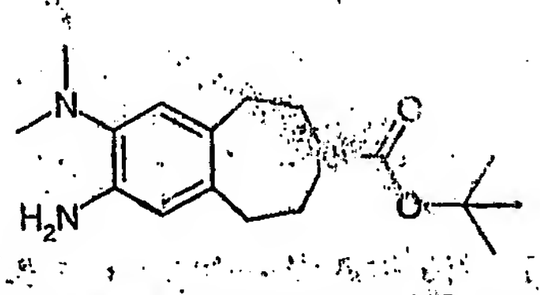
A suspension of BINAP (106 mg), palladium(II) acetate (26 mg) and caesium carbonate (555 mg) in dioxan (5 ml) was sonicated for 30 min at room temperature. To the resulting red mixture was added D15c (0.5 g) and piperidine (0.2 ml) and the mixture was heated in a Smith microwave reactor for 30 mins at 160°C. The mixture was diluted with diethyl ether (30 ml) and water (30 ml) and the layers were separated. The aqueous portion was extracted with a further portion of diethyl ether (10 ml) and the combined organic extracts were washed with saturated sodium bicarbonate solution and then dried (Na_2SO_4), filtered and evaporated. Chromatography using 0-10% EtOAc/n-hexane as eluent gave the title compound D18a (0.28 g).

7-Amino-8-piperidin-1-yl-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester (D18)

Hydrogenation of D18a (278 mg) at 50psi in ethanol (40 ml) over 10% palladium on charcoal (100 mg, paste) at room temperature afforded the title compound D18 (253 mg). MH^+ 346

Description 19

7-Amino-8-dimethylamino-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid tert-butyl ester (D19)



7-Nitro-8-dimethylamino-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester (D19a)

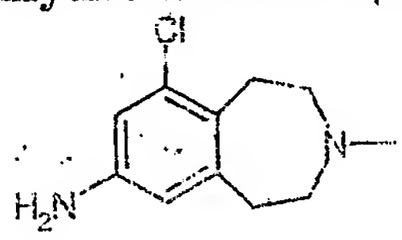
A suspension of BINAP (106 mg), palladium acetate (26 mg) and caesium carbonate (556 mg) in dioxan (5 ml) under argon was sonicated for 30 min at room temperature. To the resulting red suspension was added D15c (500 mg) and dimethylamine hydrochloride (150 mg). The mixture was then heated in a microwave reactor for 30 mins at 160°C, diluted with diethyl ether (30 ml) and washed with water (50 ml) and saturated sodium bicarbonate solution (30 ml) and then the layers separated. The organic portion was dried (Na_2SO_4), filtered and evaporated to give the title compound D19a as an oil (263 mg). MH^+ 336

7-Amino-8-dimethylamino-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid tert-butyl ester (D19)

Hydrogenation of D19a at 50 psi in ethanol over 10% palladium on charcoal at room temperature afforded the title compound D19. MH^+ 306

Description 20

9-Chloro-3-methyl-2,3,4,5-tetrahydro-1H-benzo[d] azepin-7-ylamine (D20)



3-Acetyl-7-nitro-1,2,4,5-tetrahydro-3-benzazepine (D20a)

The title compound was prepared according to a similar procedure described in J. Heterocycl. Chem. 1971 8(5) 779.

3-Acetyl-7-nitro-9-iodo-1,2,4,5-tetrahydro-3-benzazepine (D20b)

D20a (22.4 g) in trifluoromethane sulphonic acid (150 ml) was treated with N-iodosuccinimide (40 g) portionwise over 5 days. Aqueous workup gave the crude title compound D20b (25 g). MH^+ 361.

7-Nitro-9-iodo-1,2,4,5-tetrahydro-3-benzazepine (D20c)

Crude D20b (25 g) was heated to 120°C in concentrated hydrochloric acid (1 litre) for 12 h. Basic aqueous workup followed by chromatography using 5% methanol/dichloromethane as eluent gave the title compound D20c (7 g). MH^+ 319.

3-Methyl-7-nitro-9-iodo-1,2,4,5-tetrahydro-3-benzazepine (D20d)

D20c (7.3 g) was treated with formalin (37% aqueous, 20 ml) in dichloroethane (30 ml) for 0.5 h, followed by sodium triacetoxyborohydride (7 g). Chromatography using 1%

methanol/dichloromethane as eluent and recrystallisation from dichloromethane/hexane gave the title compound D20d (1.9 g). MH^+ 333.

3-Methyl-7-nitro-9-chloro-1,2,4,5-tetrahydro-3-benzazepine (D20e)

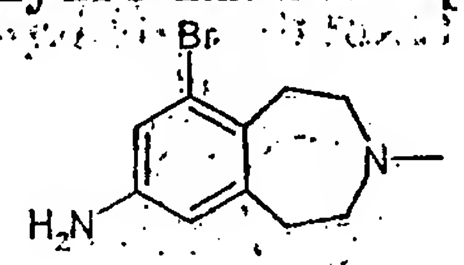
Reaction of D20d (0.8 g) with copper(I) chloride (1.68 g) in dimethylformamide (15 ml) at 120°C for 2 h followed by chromatography using 1-3% methanol/dichloromethane as eluent gave the title compound D20e (0.3 g). MH^+ 241.

9-Chloro-3-methyl-2,3,4,5-tetrahydro-1H-benzo[d] azepin-7-ylamine (D20)

Hydrogenation of D20e (0.3 g) at 1 atmosphere in ethanol over 10% rhodium on charcoal at room temperature afforded the title compound D20 (0.19 g). MH^+ 211.

Description 21

9-Bromo-3-methyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-ylamine (D21)



3-Methyl-7-nitro-9-iodo-1,2,4,5-tetrahydro-3-benzazepine (D21a)

The title compound was prepared according to the procedure described for D20d.

3-Methyl-7-nitro-9-bromo-1,2,4,5-tetrahydro-3-benzazepine (D21b)

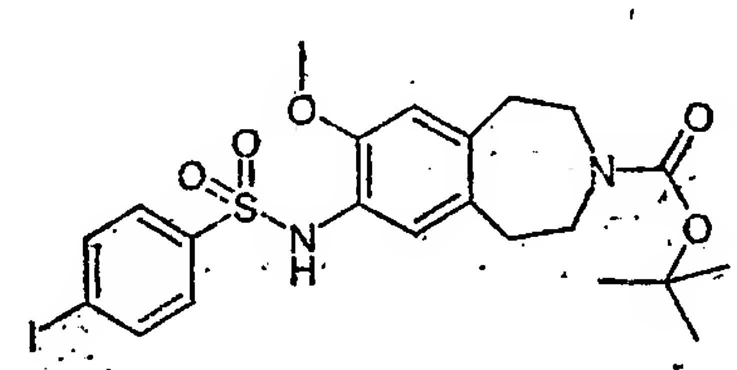
Reaction of D21a (1 g) with copper(I) bromide (3 g) in dimethylformamide ([illegible] ml) at [illegible] for 3 h followed by chromatography using 1-3% methanol/dichloromethane as eluent gave the title compound D21b (0.23 g). MH^+ 286.

9-Bromo-3-methyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-ylamine (D21)

Reduction of the nitro group was achieved by treating D21b (0.23 g) in ethanol (6 ml), water (3 ml) and acetic acid (0.5 ml) with iron powder (180 mg) at reflux for 1 h. Basic aqueous workup and filtering gave the title compound D21 (0.19 g). MH^+ 256.

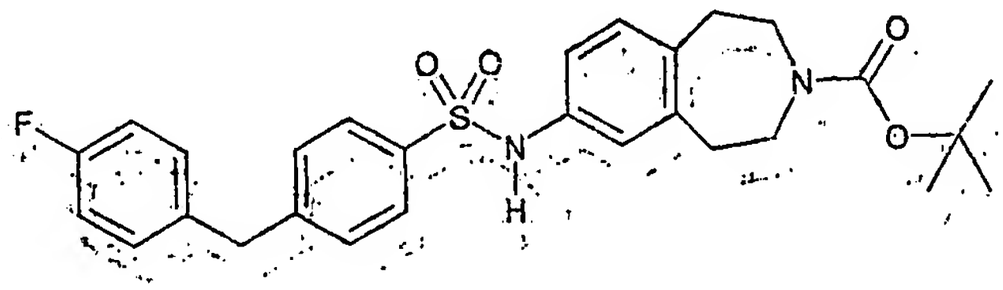
Description 22

7-(4-Iodo-benzenesulfonylamino)-8-methoxy-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester (D22)



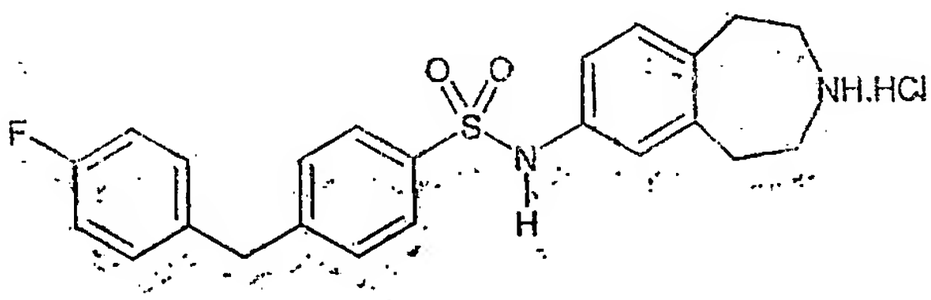
7-Amino-8-methoxy-1,2,4,5-tetrahydro-3-benzazepine-3-carboxylic acid tert-butyl ester (D5) (1.9 g, 6.5 mmol) was treated with pipsyl chloride (2.2 g, 7.2 mmol) in dichloromethane (20 ml) and pyridine (35 ml). The mixture was stirred for 13 h and the solvents evaporated. Chromatography on silica eluting with dichloromethane afforded the title compound D22 (2.8 g). M^+ [illegible] + 2H = 403, ^1H NMR ($CDCl_3$) δ 7.70 (2H, d, J = 8.6 Hz), 7.43 (2H, d, J = 8.6 Hz), 6.[illegible] (1H, s), [illegible] (1H, s), [illegible] (1H, s), [illegible] (4H, m), 2.80 (4H, m), 1.47 (9H, s).

Description 23
7-[4-(4-Fluorobenzyl)benzenesulfonylamino]-1,2,4,5-tetrahydro-benzo[*d*]azepine-3-carboxylic acid *tert*-butyl ester (D23)



To a solution of the iodo compound D7 (0.129 g, 0.244 mmol, 1.0 eq) in anhydrous tetrahydrofuran (2 ml) under argon at room temperature was added dropwise 4-fluorobenzylzinc chloride (1.1 ml 0.5M in tetrahydrofuran, 0.537 mmol, 2.2 eq). The resultant solution was degassed by bubbling argon through the solution for 5 min then $Pd(PPh_3)_4$ was added and the solution heated at 50°C for 4h before allowing to cool to room temperature. Saturated aqueous NH_4Cl solution was added (10 ml) and the mixture extracted with EtOAc (2 × 10 ml). The organic layer was washed with brine (15 ml), dried over $MgSO_4$ and evaporated to dryness. Purification by chromatography over silica gel, eluting with 25% EtOAc-petrol afforded the title compound D23 as a pale yellow solid (0.120 g, 97%). MH^+ 511. ^1H NMR δ $CDCl_3$ 1.47 (9H, s), 2.79 (4H, m), 3.48 (4H, m), 3.97 (2H, s), 6.44 (1H, s), 6.81 (2H, br.s), 6.82-7.25 (5H, m), 7.22 (2H, d), 7.67 (2H, d).

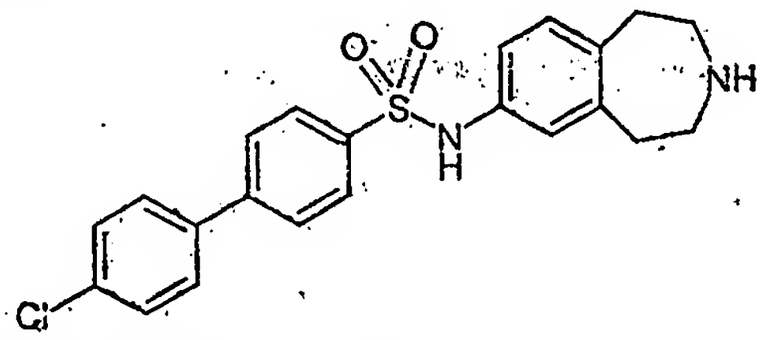
Description 24
4-(4-Fluorobenzyl)-*N*-(2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yl)benzenesulfonamide hydrochloride (D24)



A solution of the Boc-protected amine D23 (0.104 g, 0.204 mmol, 1.0 eq) in 1,4 dioxan (3 ml) and 4M HCl in dioxan (2 ml, excess) was stirred at room temperature under argon for 6 h then evaporated to dryness, affording the desired compound D24 as a white solid (0.086 g, 96%). MH^+ 411.

Example 1

4-(4-Chloro-phenyl)-*N*-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide (E1)



4-(4-Chloro-phenyl)-*N*-[3-(2,2,2-trifluoro-ethanoyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl]-benzenesulfonamide (E1a)

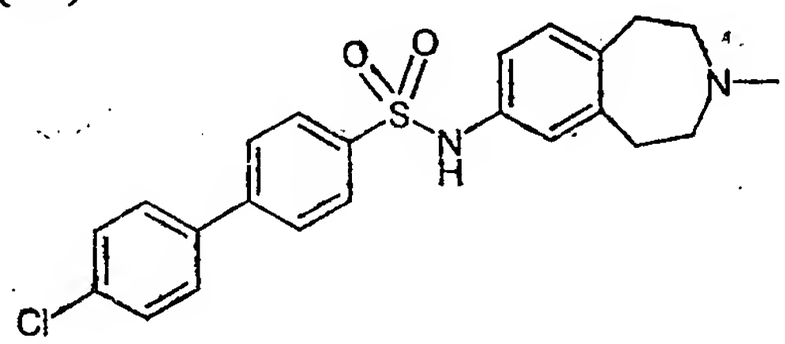
A solution of 4'-chloro-biphenyl-4-sulfonyl chloride D8 (1.24 g, 4.3 mmol) in dichloromethane 910 ml) was added dropwise to a solution of D1 (1.0 g, 3.9 mmol) in pyridine (20 ml) at 0°C. The mixture was stirred at room temperature for 18 h, then poured onto brine and extracted with ethyl acetate (2 x). The combined organic layer was washed with citric acid, sodium bicarbonate solution and brine, then dried and evaporated to afford the crude product. Chromatography on silica, eluting with 30% ethyl acetate/hexane afforded the product E1a (1.5 g). MH^+ 509

4-(4-Chloro-phenyl)-*N*-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide (E1)

The compound E1a was dissolved in 2M ammonia in methanol (24 ml) and water (6 ml) added to the stirred solution. Stirring was continued for 18 h, then the solution evaporated to dryness. Application of the crude product to an SCX ion exchange cartridge, followed by elution with methanol followed by 1% ammonia in methanol afforded the title compound E1 (0.85 g). MH^+ 413. ^1H NMR: δ $CDCl_3$ 2.8-2.9 (8H, m), 6.8 (2H, m), 6.96 (1H, d), 7.43 (2H, d), 7.50 (2H, d), 7.61 (2H, d), 7.81 (2H, d).

Example 2

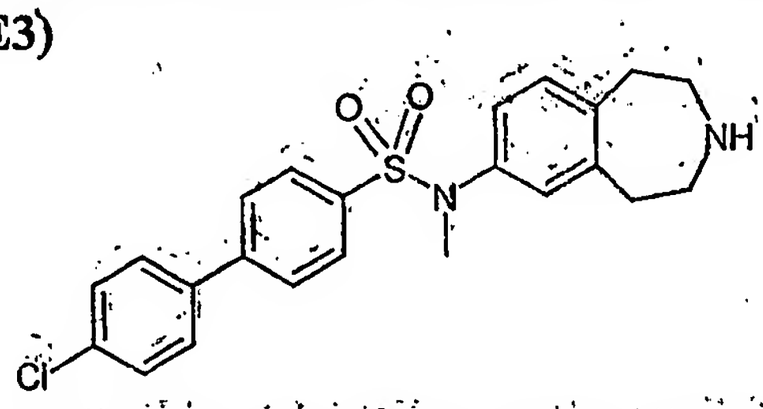
4-(4-Chloro-phenyl)-*N*-(3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide (E2)



A solution of E1 (144 mg, 0.35 mmol) in dichloroethane (10 ml) was treated with formalin (0.3 ml) followed by sodium triacetoxyborohydride (250 mg). The mixture was stirred for 18 h, then added to sodium bicarbonate solution and extracted with dichloromethane. The combined organic extracts were washed with brine, dried and evaporated to afford the crude product. Chromatography on silica, eluting with 2% methanol in dichloromethane containing 0.5% aqueous ammonia, afforded the title compound E2 (140 mg). MH^+ 425. ^1H NMR: δ $CDCl_3$ 2.35 (3H, s), 2.53 (4H, m), 2.86 (4H, m), 6.83 (2H, m), 6.96 (1H, d), 7.44 (2H, d), 7.51 (2H, d), 7.61 (2H, d), 7.81 (2H, d).

Example 3

4-(4-Chloro-phenyl)-*N*-methyl-*N*-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide (E3)



4-(4-Chloro-phenyl)-*N*-methyl-*N*-[3-(2,2,2-trifluoro-ethanoyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl]-benzenesulfonamide (E3a)

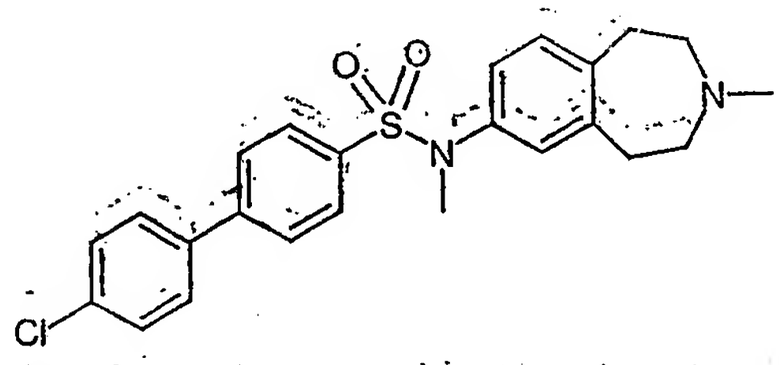
The trifluoroacetamide E1a (500 mg, 1 mmol) was dissolved in dry tetrahydrofuran (15 ml) containing triphenylphosphine (330 mg) and dry methanol (200 mg). To this stirred solution was added di-isopropylazodicarboxylate (250 mg, 1.2 mmol) and the mixture stirred at room temperature for 18 h. The solvent was then evaporated and the residue chromatographed on silica using 20% ethyl-acetate/hexane as eluant to afford the product E3a (640 mg). MH^+ 523.

4-(4-Chloro-phenyl)-*N*-methyl-*N*-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide (E3)

Deprotection of the compound D3a using a procedure similar to that for compound E1b afforded the title compound E3 (370 mg). MH^+ 427. ^1H NMR: δ $CDCl_3$ 2.79 (8H, 3.18 (3H, s), 6.79 (1H, m), 6.91 (1H, s), 7.01 (1H, d), 7.46 (2H, d), 7.53 (2H, d), 7.53 (4H, s).

Example 4

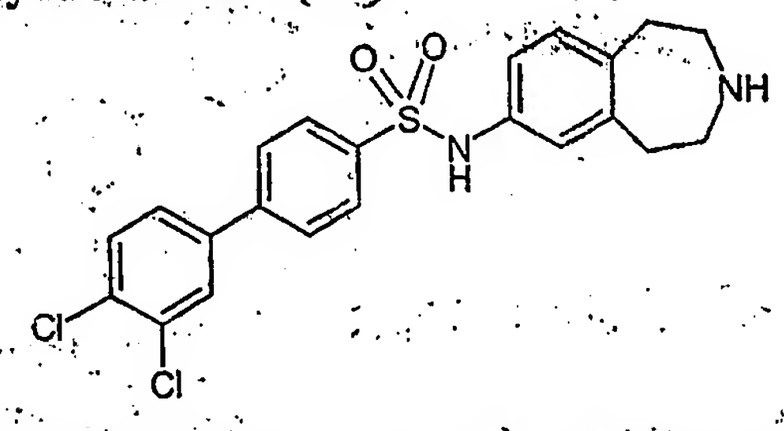
4-(4-Chloro-phenyl)-*N*-methyl-*N*-(3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide (E4)



The title compound was prepared from E3 using a procedure similar to that for compound E2. MH^+ 441. ^1H NMR: δ $CDCl_3$ 2.37 (3H, s), 2.57 (4H, s), 2.90 (4H, s), 3.18 (3H, s), 6.80 (1H, dd), 6.92 (1H, dd), 7.01 (1H, d), 7.45 (2H, d), 7.53 (2H, d), 7.63 (4H, s).

Example 5

4-(3,4-Dichloro-phenyl)-*N*-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide hydrochloride (E5)



7-(3',4'-Dichloro-biphenyl-4-sulfonylamino)-1,2,4,5-tetrahydro-3-benzazepine-3-carboxylic acid *tert*-butyl ester (E5a)

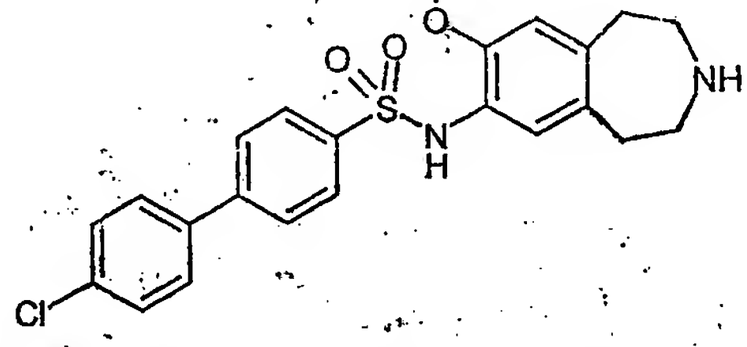
A solution of the iodo intermediate D7 (0.53 g, 1 mmol) was dissolved in a mixture of ethanol (3 ml), toluene (10 ml) and 2M aqueous potassium carbonate solution (3 ml) containing 3,4-dichlorobenzeneboronic acid (0.29 g, 1.5 mmol). This mixture was rigorously degassed and an argon atmosphere introduced. Tetrakis(triphenylphosphine)palladium (0.1 g) was added, and the mixture heated to 90°C for 18 h. After cooling, the solution was poured onto brine and extracted with ethyl acetate (2 x). The organic layer was washed with brine dried and evaporated to afford the crude product. Chromatography on silica, eluting with 10-25% ethyl acetate/hexane afforded the title compound E5a (0.57 g). MH^+ 548.

4-(3,4-Dichloro-phenyl)-*N*-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide hydrochloride (E5)

The title compound was prepared from compound E5a by treatment with a solution of ethanolic hydrogen chloride, followed by the addition of ether to precipitate the product E5. MH^+ 447. ^1H NMR: δ DMSO 2.98 (4H, s), 3.08 (4H, s), 6.95 (2H, m), 7.06 (1H, d), 7.74 (2H, m), 7.8-7.9 (4H, m), 8.01 (1H, dd).

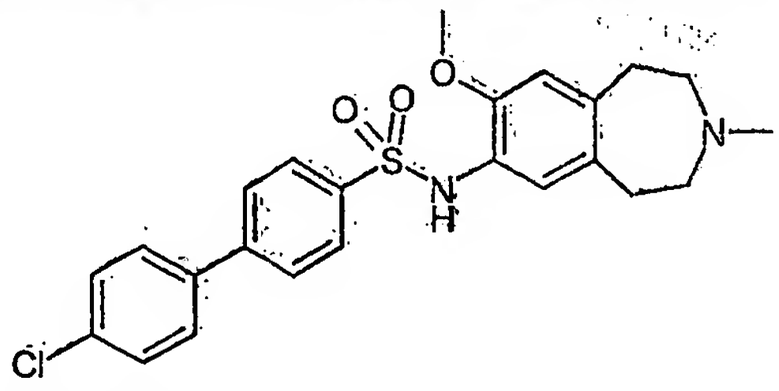
Example 6

4-(4-Chloro-phenyl)-*N*-(8-methoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide hydrochloride (E6)



The title compound E6 was prepared from D5 and D8 using a procedure similar to that for compounds E1a and E5b. MH^+ 443. ^1H NMR DMSO δ: 3.00 (4H, m), 3.11 (4H, m), 3.40 (3H, s), 6.79 (1H, s), 7.09 (1H, s), 7.56 (2H, d, J = 8.5Hz), 7.74 (2H, d, J = 7.1Hz), 7.77 (2H, d, J = 7.1Hz), 7.83 (2H, d, J = 8.5Hz), 9.14 (2H, s), 9.53 (1H, s)

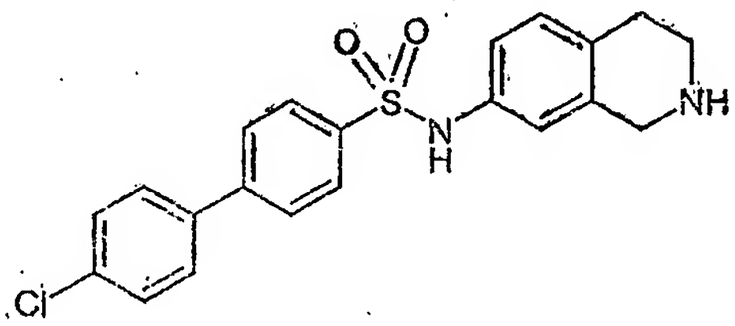
Example 7
4-(4-Chloro-phenyl)-*N*-(8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide hydrochloride (E7)



The title compound was prepared from E6 using a procedure similar to that for E2, and the product isolated as the hydrochloride salt. MH^+ 457. ^1H NMR:$\delta CDCl_3$ 2.35 (3H, s), 2.50 (4H, m), 2.84 (4H, m), 3.57 (3H, s), 6.48 (1H, s), 6.9 (1H, b s), 7.31 (1H, s), 7.4-7.59 (6H, m), 7.80 (2H, m).

Examples 11-41 and 74-154 and 188-209 and 216-217 were prepared using analogous procedures to Examples 1-7 and 42-47 using the appropriate starting materials, with the products being isolated as either the free bases or hydrochloride salts. All ^1H NMR are consistent with the structures shown.

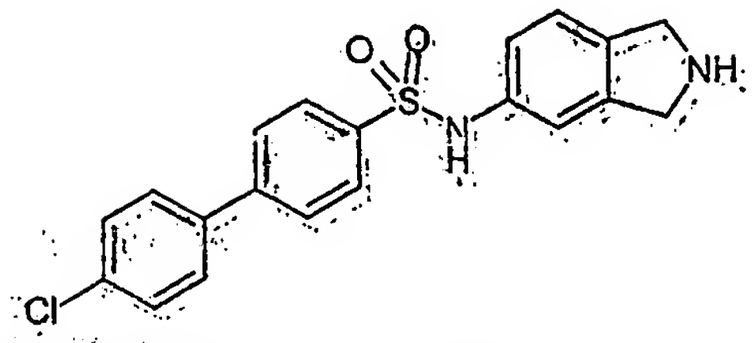
Example 8
4-(4-Chloro-phenyl)-*N*-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-benzenesulfonamide (E8)



The title compound E8 was prepared from D4 and D8 using a procedure similar to that for compounds E1a and E5b. MH^+ 399. ^1H NMR: δ DMSO-d^6 2.5 (2H,m), 2.8 (2H,m), 3.7 (2H, m), 6.77 (1H, ms), 6.9 (2H, m), 7.5 (2H, d), 7.7 (2H, d), 7.8(4H, m).

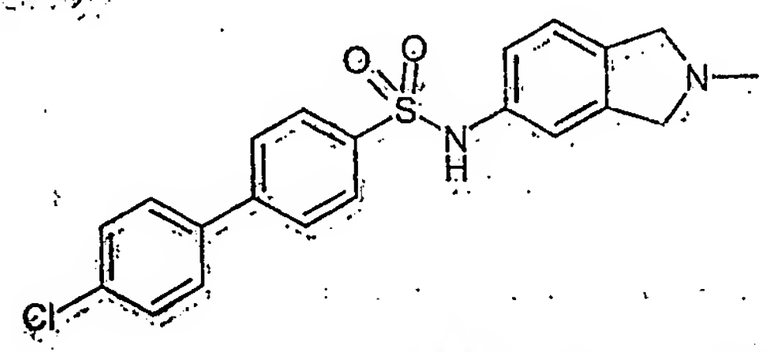
Examples 48-73 and 155-166 were prepared using analogous procedures to Examples 1-8 using the appropriate starting materials, with the products being isolated as either the free bases or hydrochloride salts. All ^1H NMR are consistent with the structures shown.

Example 9
4-(4-Chloro-phenyl)-*N*-(2,3-dihydro-1*H*-isoindol-5-yl)-benzenesulfonamide hydrochloride (E9)



The title compound E9 was prepared from D6 and D8 using a procedure similar to that for compounds E1a and E5b. MH^+ 385. ^1H NMR: δ DMSO-d^6 4.4 (4H, m), 7.11 (1H, d), 7.25 (2H, m), 7.55 (2H, d), 7.73 (2H, m), 7.86 (4H, s), 9.7 (2H, m), 10.55 (1H, m).

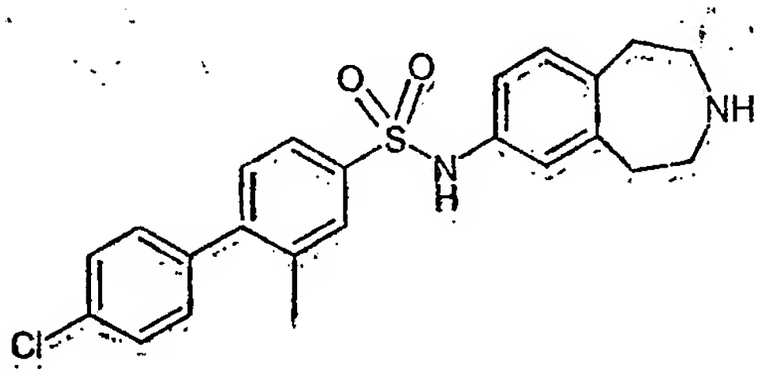
Example 10
4-(4-Chloro-phenyl)-*N*-(2-methyl-2,3-dihydro-1*H*-isoindol-5-yl)-benzenesulfonamide (E10)



The title compound E10 was prepared from E9 using a procedure similar to that for compound E2. MH^+ 399. ^1H NMR: δ DMSO-d^6 0.86 (3H, m), 1.2 (2H, m), 1.5 (2H, m), 2.41 (3H, s) 2.6 (2H, m), 3.68 (4H, s), 6.87 (1H, d), 6.93 (1H, s), 7.05 (2H, d), 7.3 (2H, d), 7.64 (2H, d).

Examples 167-174 were prepared using analogous procedures to Examples 1-6, and as described herein, using the appropriate starting materials, with products being isolated as either the free bases or hydrochloride salts. All ^1H NMR are consistent with the structures shown.

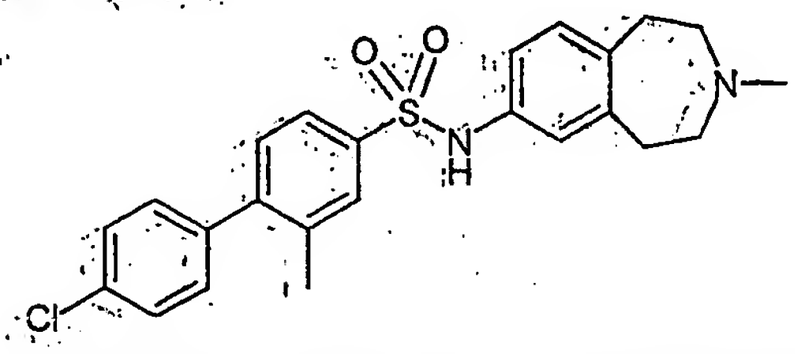
Example 42
4-(4-Chloro-phenyl)-3-methyl-*N*-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide hydrochloride (E42)



The title compound E42 was prepared from D3 and D9 using a procedure similar to that for compounds E1a and E5b. MH^+ 427. ^1H NMR: δ DMSO-d^6 2.26 (3H,s), 3.0 (4H, m), 3.15 (4H, m), 6.95 (2H, m), 7.07 (1H, d), 7.4 (3H, m), 7.5 (2H, d), 7.63 (1H, d), 7.74 (1H, s), 9.1 (1H, br), 10.3 (1H, br)

Example 43

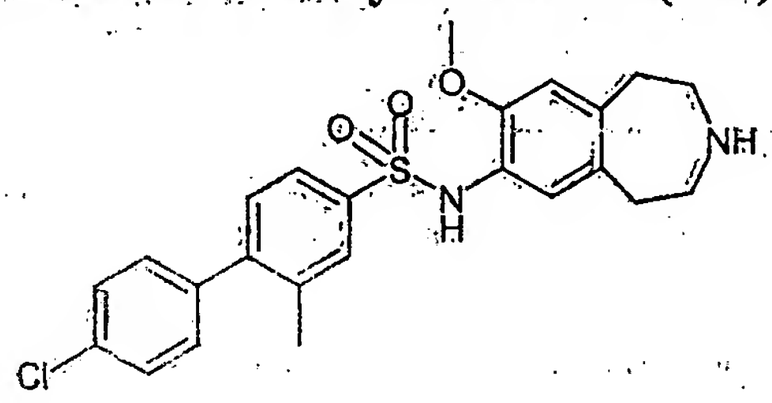
4-(4-Chloro-phenyl)-3-methyl-*N*-(3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide (E43)



The title compound was prepared from E42 using a procedure similar to that for compound E2. MH^+ 441. ^1H NMR: δ $CDCl_3$ 2.24 (3H,s), 2.34 (3H,s), 2.6 (4H, m), 2.8 (4H, m), 6.85 (2H, m), 7.0 (1H, d), 7.2 (3H, m), 7.4(2H, m), 7.6 (2H, m).

Example 44

4-(4-Chloro-phenyl)-3-methyl-*N*-(8-methoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide hydrochloride (E44)

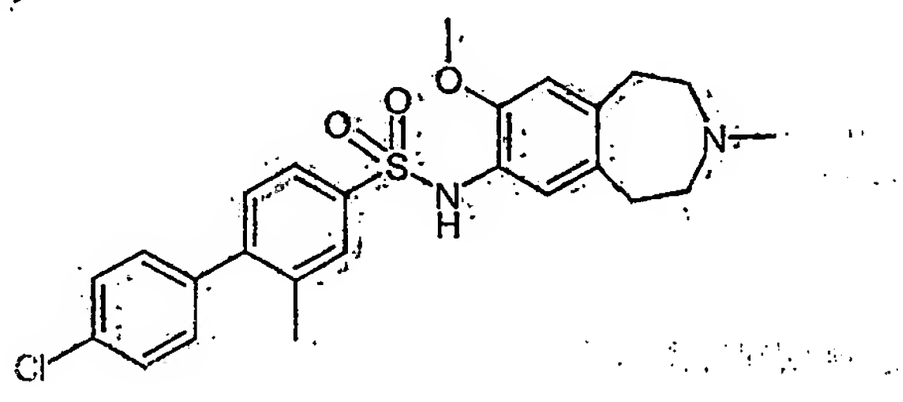


The title compound E44 was prepared from D5 and D10 using a procedure similar to for compounds E1a and E5b. MH^+ 457. ^1H NMR: δ DMSO-d^6 2.51 (3H, s), 3.23 (8H, b s); 3.69 (3H, s), 6.57 (1H, s), 6.98 (1H, s), 7.20 (2H, m), 7.38 (3H, m), 7.60 (1H, d), 7.67 (1H, s).

Example 45

4-(4-Chloro-phenyl)-3-methyl-*N*-(8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide (E45)

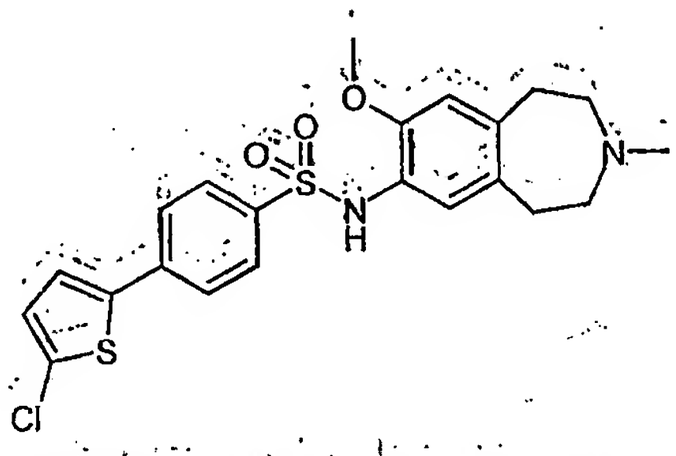
The title compound E44 was prepared from E46 using a procedure similar to that for compound E2. MH^+ 471. ^1H NMR: δ $CDCl_3$ 2.23 (3H, s), 2.50 (3H, s), 2.74 (4H, s), 2.99 (4H, s), 3.64 (3H, s), 6.52 (1H, s), 7.17 (2H, d), 7.26 (1H, d), 7.31 (1H, s), 7.38 (2H, d), 7.41 (1H, m), 7.66 (1H, m).



Examples 46-47 were prepared using analogous procedures to E44 and E45 using the appropriate starting materials, with the products being isolated as either the free bases or hydrochloride salts. All ^{1}H NMR are consistent with the structures shown.

Example 107

4-(5-Chloro-thiophen-2-yl)-N-(8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-benzo[d]azepin-7-yl)-benzenesulfonamide (E107)



7-[4-(5-Chloro-thiophen-2-yl)-benzenesulfonylamino]-8-methoxy-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester (E107a)

7-(4-Iodo-benzenesulfonylamino)-8-methoxy-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester D22 (0.28 g; 0.5 mmol) was treated with 5-chloro-thiophene-2-boronic acid under standard Suzuki conditions (see D9) followed by aqueous workup and chromatography to give the title compound E107a (0.22 g). M^+-$C(CH_3)_3$ + H 493/495.

4-(5-Chloro-thiophen-2-yl)- N-(8-methoxy-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-benzenesulfonamide hydrochloride (E107b)

7-[4-(5-Chloro-thiophen-2-yl)-benzenesulfonylamino]-8-methoxy-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester E107a (0.22 g) was treated with 4M HCl in dioxan solution for 2 h. Diethyl ether was added and the precipitate filtered to give the title compound E107b as a colourless solid (0.19 g). M^+ 447/449

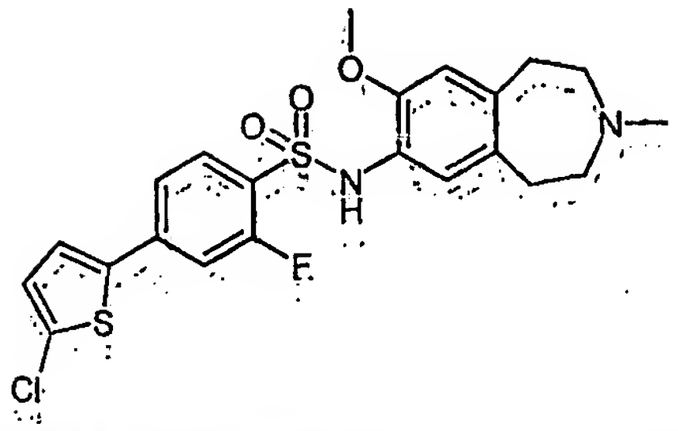
4-(5-Chloro-thiophen-2-yl)-N-(8-methoxy-3-methyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-benzenesulfonamide (E107)

4-(5-Chloro-thiophen-2-yl)- N-(8-methoxy-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-benzenesulfonamide (E107b) (0.19 g) in dichloroethane (8 ml) was treated with triethylamine (0.9 ml) and formalin solution (37% aqueous, 0.3 ml) followed by sodium triacetoxyborohydride (250 mg). The mixture was shaken vigorously for 1 h and then diluted with dichloromethane (5 ml) and sodium bicarbonate solution (3 ml). The layers were separated and the organic portion evaporated. Chromatography on silica eluting with 10% methanol/ dichloromethane afforded the title compound E107 (57 mg). M^+ 463/465

^{1}H NMR ($CDCl_3$) δ 7.71 (2H, d, J = 8.5 Hz), 7.50 (2H, d, J = 8.5 Hz), 7.29 (1H, s), 7.15 (1H, d, J = 3.9 Hz), 6.92 (1H, d, J = 3.9 Hz), 6.86 (1H, s), 6.48 (1H, s), 3.57 (3H, s), 2.88 (4H, m), 2.57 (4H, m), 2.39 (3H, s).

Example 216

4-(5-Chloro-thiophen-2-yl)-2-fluoro-N-(8-methoxy-3-methyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-benzenesulfonamide (E216)



7-(4-Bromo-2-fluoro-benzenesulfonylamino)-8-methoxy-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester (E216a)

7-Amino-8-methoxy-1,2,4,5-tetrahydro-3-benzazepine-3-carboxylic acid *tert*-butyl ester D5 (391 mg) was treated with 2-fluoro-4-bromobenzenesulfonyl chloride (460 mg) in dichloromethane (15 ml) and pyridine (9 ml). The mixture was stirred for 3 h and the solvents evaporated. Chromatography on silica eluting with dichloromethane afforded the title compound E216a (740 mg). M-H 575

7-[2-Fluoro-4-(5-chloro-thiophen-2-yl)-benzenesulfonylamino]-8-methoxy-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester (E216b)

7-(4-Iodo-2-fluoro-benzenesulfonylamino)-8-methoxy-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester E216a (320 mg) was treated with 5-chloro-thiophene-2-boronic acid (135 mg) under standard Suzuki conditions (see D9) followed by aqueous workup and chromatography to give the title compound E216b (140 mg). M-H 565

2-Fluoro-4-(5-Chloro-thiophen-2-yl)-N-(8-methoxy-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-benzenesulfonamide hydrochloride (E216c)

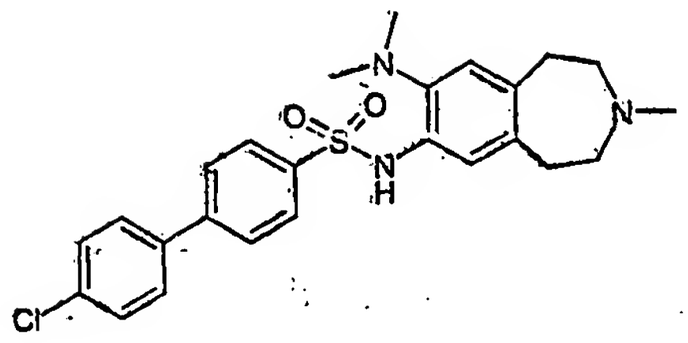
7-[2-Fluoro-4-(5-chloro-thiophen-2-yl)-benzenesulfonylamino]-8-methoxy-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester (E216b) (140 mg) was treated with ethanolic HCl solution (6 ml) for 2 h. The solvent was evaporated to give the title compound E216c as a colourless solid (100 mg).M+H 445

4-(5-Chloro-thiophen-2-yl)-2-fluoro-N-(8-methoxy-3-methyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-benzenesulfonamide (E216)

2-Fluoro-4-(5-chloro-thiophen-2-yl)-N-(8-methoxy-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-benzenesulfonamide E216c (100 mg) in dichloroethane (8 ml) was treated with formalin solution (37% aqueous, 0.2 ml) followed by sodium triacetoxyborohydride (70 mg). The mixture was shaken vigorously for 1 h and then diluted with dichloromethane (5 ml) and sodium bicarbonate solution (5 ml). The layers were separated and the organic portion was evaporated. Chromatography on silica eluting with 10% methanol/dichloromethane afforded the title compound E216. M+H 459. ^{1}H NMR (DMSO-d^6) (HCl salt) δ 10.78 (1H, s), 9.76 (1H, s), 7.79 (2H, d, J = 11.5 Hz), 7.66 (1H, d, J = 4 Hz), 7.59 (1H, t, J = 8 Hz), 7.47 (1H, d, J = 8 Hz), 7.26 (1H, d, J = 4 Hz), 7.08 (1H, s), 6.81 (1H, s), 3.53 (2H, m), 3.42 (3H, s), 3.20 (2H, m), 2.92 (4H, m), 2.77 (3H, d, J = 4.6 Hz).

Example 217

4'-Chloro-biphenyl-4-sulfonic acid (dimethylamino-methyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-amide (E217)



7-(4'-Chloro-biphenyl-4-sulfonylamino)-8-dimethylamino-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid dimethyl-ethyl ester (E217a)

7-Amino-8-dimethylamino-1,2,4,5-tetrahydro-3-benzazepine-3-carboxylic acid *tert*-butyl ester (D19) (120 mg) was treated with 4'-chlorobiphenyl-4-sulfonyl chloride (136 mg) in dichloromethane (5 ml) and pyridine (0.05 ml). Mixture stirred for 3 h and the solvents evaporated. Chromatography on silica eluting with 20% ethyl acetate/hexane afforded the title compound E217a (175 mg). M+H 556/558

4'-Chloro-biphenyl-4-sulfonic acid (8-dimethylamino-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-amide hydrochloride (E217b)

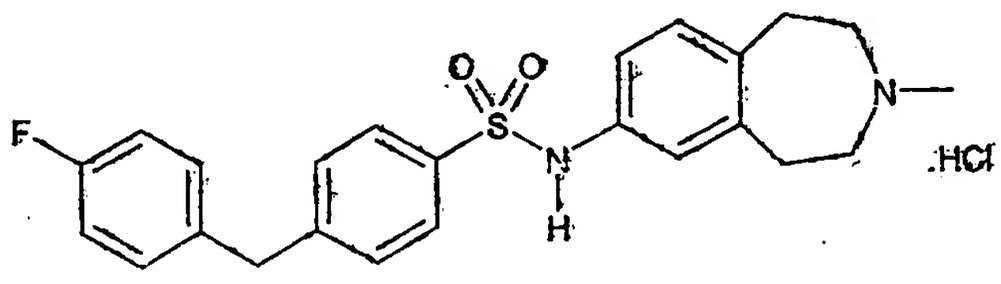
7-(4'-Chloro-biphenyl-4-sulfonylamino)-dimethylamino-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid dimethyl-ethyl ester (E217a) (175 mg) was treated with ethanolic HCl solution (4 ml) for 2 h. The solvent was evaporated to give the title compound E217b as a colourless solid (120 mg). M+H 456/458

4'-Chloro-biphenyl-4-sulfonic acid (dimethylamino-methyl-[illegible]-tetrahydro-benzo[d]azepin-7-yl)-amide (E217)

4'-Chloro-biphenyl-4-sulfonic acid (8-dimethylamino-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-amide hydrochloride (E217b) (75 mg) in dichloroethane (3 ml) was treated with formalin solution (37% aqueous, 1 ml) followed by sodium triacetoxyborohydride (48 mg). The mixture was shaken vigorously for 1 h and then diluted with dichloromethane (10 ml) and sodium bicarbonate solution (10 ml). The layers were separated and the organic portion was evaporated. Chromatography on silica eluting with 10% methanol/dichloromethane afforded the title compound E217 (65 mg). M+H 470/472. ^{1}H NMR ($CDCl_3$) 8.05 (2H, s), 7.90 (2H, d, J = 6.7 Hz), 7.60 (2H, d, J = 6.7 Hz), 7.47 (2H, d, J = 6.4 Hz), 7.42 (2H, d, J = 6.4 Hz), 7.35 (1H, s), 6.83 (1H, s), 2.87 (2H, m), 2.81 (2H, m), 2.53 (4H, m), 2.40 (6H, s), 2.35 (3H, s).

Example 210

4-(4-Fluorobenzyl)-*N*-(3-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yl)benzenesulfonamide hydrochloride (E210)



To a suspension of salt D24 (0.083 g, 0.186 mmol, 1.0 eq) in 1,2-dichloroethane (3.5 ml) at room temperature was added triethylamine (26 µl, 0.186 mmol, 1.0 eq) followed by 37%

aqueous formaldehyde solution (0.6 ml, excess). After vigorous stirring for 5 min. sodium triacetoxyborohydride (0.090 g, excess) was added portionwise. After 2 h saturated aqueous sodium bicarbonate solution (10 ml) and dichloromethane (10 ml) were added and the layers separated. The organic layer was evaporated to dryness, affording the free base as a pale yellow solid (0.077g, 97%). The solid was dissolved in methanol, 1M HCl added (1.05 eq) and the mixture concentrated to dryness, giving the title compound E210 as an off-white solid. MH^+ 425. ^1H NMR δ DMSO-d^6 2.43 (3H, s), 2.82 (4H, m), 3.51 (4H, m), 4.04 (2H, s), 6.93-7.35 (7H, m), 7.39 (2H, d), 7.73 (2H, d), 10.28 (1H, s), 10.75 (1H, s).

Examples 175-187 were prepared using analogous procedures to Example 188 using the appropriate starting materials and Examples 211-215 using analogous procedures to Descriptions 23-24 and Example 210, with the products being isolated as either free bases or hydrochloride salts. All ^1H NMR are consistent with the structures shown.

All of the compounds listed below in Table 1 relate to compounds of the formula (II):

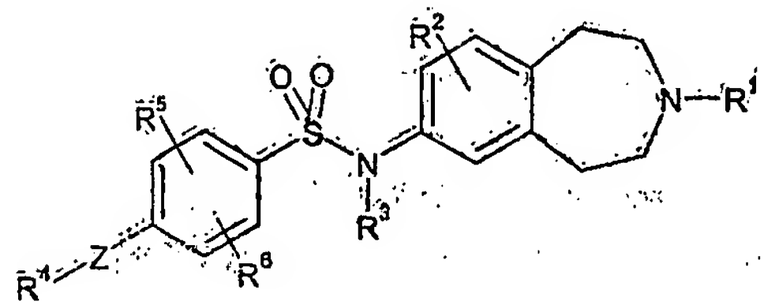


Table 1

Example	R^1	R^2	R^3	R^4	R^5	R^6	Z	MH^+
1	H	H	H	4-ClPh	H	H	bond	413
2	Me	H	H	4-ClPh	H	H	bond	427
3	H	H	Me	4-ClPh	H	H	bond	427
4	Me	H	Me	4-ClPh	H	H	bond	441
5	H	H	H	3,4-diClPh	H	H	bond	447
6	H	8-MeO	H	4-ClPh	H	H	bond	443
7	Me	8-MeO	H	4-ClPh	H	H	bond	457
11	H	8-Br	H	4-ClPh	H	H	bond	493
12	Me	H	H	2-ClPh	H	H	bond	427
13	H	H	H	3-ClPh	H	H	bond	413
14	Me	H	H	3-ClPh	H	H	bond	427
15	Me	H	H	3,4-diClPh	H	H	bond	461
16	Me	H	H	2,4-diClPh	H	H	bond	461
17	H	H	H	4-BrPh	H	H	bond	458
18	Me	H	H	4-BrPh	H	H	bond	472
19	Me	H	H	4-MePh	H	H	bond	407
20	H	H	H	3-MePh	H	H	bond	393
21	Me	H	H	3-MePh	H	H	bond	407
22	H	H	H	2-MePh	H	H	bond	393
23	Me	H	H	2-MePh	H	H	bond	407
24	Me	H	H	4-CF_3Ph	H	H	bond	461
25	Me	H	H	4-OCF_3Ph	H	H	bond	477
26	Me	H	H	4-MeSPh	H	H	bond	439
27	Me	H	H	4-t-BuPh	H	H	bond	449
28	H	H	H	4-CNPh	H	H	bond	405
29	Me	H	H	4-CNPh	H	H	bond	419
30	Me	H	H	4-MeOPh	H	H	bond	423
31	Me	H	H	4-FPh	H	H	bond	411
32	Me	H	H	2-thienyl	H	H	bond	399

Table 1 (continued)

Example	R^1	R^2	R^3	R^4	R^5	R^6	Z	MH^+
33	Me	H	H	5-Cl-2-thienyl	H	H	bond	434
34	H	H	H	3-thienyl	H	H	bond	385
35	Me	H	H	3-thienyl	H	H	bond	399
36	Me	H	H	2-naphthyl	H	H	bond	443
37	H	H	H	2-benzofuranyl	H	H	bond	419
38	H	H	H	4-pyridyl	H	H	bond	379
39	Et	H	H	4-ClPh	H	H	bond	441
40	n-Pr	H	H	4-ClPh	H	H	bond	455
41	i-Pr	H	H	4-ClPh	H	H	bond	455
42	H	H	H	4-ClPh	3-Me	H	bond	427
43	Me	H	H	4-ClPh	3-Me	H	bond	441
44	H	8-OMe	H	4-ClPh	3-Me	H	bond	457
45	Me	8-OMe	H	4-ClPh	3-Me	H	bond	471
46	H	8-Br	H	4-ClPh	3-Me	H	bond	506
47	Me	8-Br	H	4-ClPh	3-Me	H	bond	520
74	Me	H	H	4-NO_2Ph	H	H	bond	438
75	H	H	H	3-furanyl	H	H	bond	369
76	Me	H	H	3-furanyl	H	H	bond	383
77	Me	H	H	4-ClPh	H	H	O	443
78	H	8-MeO	H	Ph	H	H	bond	409
79	Me	8-MeO	H	Ph	H	H	bond	423
80	H	8-MeO	H	3-ClPh	H	H	bond	443
81	Me	8-MeO	H	3-ClPh	H	H	bond	457
82	H	8-MeO	H	3,4-diClPh	H	H	bond	478
83	Me	8-MeO	H	3,4-diClPh	H	H	bond	492
84	H	8-MeO	H	2,4-diClPh	H	H	bond	478
85	Me	8-MeO	H	2,4-diClPh	H	H	bond	492
86	H	8-MeO	H	2-Me-4-ClPh	H	H	bond	457
87	Me	8-MeO	H	2-Me-4-ClPh	H	H	bond	471
88	H	8-MeO	H	4-FPh	H	H	bond	427
89	Me	8-MeO	H	4-FPh	H	H	bond	441
90	H	8-MeO	H	4-CF_3Ph	H	H	bond	477
91	Me	8-MeO	H	4-CF_3Ph	H	H	bond	491
92	H	8-MeO	H	4-OCF_3Ph	H	H	bond	493
93	Me	8-MeO	H	4-OCF_3Ph	H	H	bond	507
94	H	8-MeO	H	4-MeOPh	H	H	bond	439
95	Me	8-MeO	H	4-MeOPh	H	H	bond	453
96	H	8-MeO	H	4-CNPh	H	H	bond	434

Table 1 (continued)

Example	R^1	R^2	R^3	R^4	R^5	R^6	Z	MH^+
97	Me	8-MeO	H	4-CNPh	H	H	bond	448
98	H	8-MeO	H	4-(NMe_2)Ph	H	H	bond	452
99	Me	8-MeO	H	4-(NMe_2)Ph	H	H	bond	466
100	H	8-MeO	H	Ph	H	H	O	425
101	Me	8-MeO	H	Ph	H	H	O	439
102	H	8-MeO	H	4-ClPh	H	H	O	459
103	Me	8-MeO	H	4-ClPh	H	H	O	473
104	H	8-MeO	H	2-thienyl	H	H	bond	415
105	Me	8-MeO	H	2-thienyl	H	H	bond	429
106	H	8-MeO	H	5-Cl-2-thienyl	H	H	bond	449
107	Me	8-MeO	H	5-Cl-2-thienyl	H	H	bond	463
108	H	8-MeO	H	3-thienyl	H	H	bond	415
109	Me	8-MeO	H	3-thienyl	H	H	bond	429
110	H	8-MeO	H	3-furanyl	H	H	bond	399
111	Me	8-MeO	H	3-furanyl	H	H	bond	413
112	H	8-MeO	H	4-pyridyl	H	H	bond	410
113	Me	8-MeO	H	4-pyridyl	H	H	bond	424
114	H	H	H	4-ClPh	3-F	H	bond	431
115	Me	H	H	4-ClPh	3-F	H	bond	445
116	H	H	H	4-ClPh	3-Cl	H	bond	448
117	H	8-EtO	H	4-ClPh	H	H	bond	457
118	Me	8-EtO	H	4-ClPh	H	H	bond	471
119	H	8-i-PrO	H	4-ClPh	H	H	bond	471
120	Me	8-i-PrO	H	4-ClPh	H	H	bond	485
121	H	8-EtO	H	4-ClPh	3-Me	H	bond	472
122	Me	8-EtO	H	4-ClPh	3-Me	H	bond	486
123	H	8-i-PrO	H	4-ClPh	3-Me	H	bond	486
124	Me	8-i-PrO	H	4-ClPh	3-Me	H	bond	500
125	H	8-i-PrO	H	2-thienyl	H	H	bond	443
126	H	8-i-PrO	H	3-thienyl	H	H	bond	443
127	H	8-i-PrO	H	3-furanyl	H	H	bond	427
128	H	8-i-PrO	H	4-FPh	H	H	bond	455
129	H	8-i-PrO	H	4-MeOPh	H	H	bond	467
130	H	8-i-PrO	H	4-CF_3OPh	H	H	bond	521
131	H	8-i-PrO	H	2-Me-4-ClPh	H	H	bond	486
132	H	8-i-PrO	H	3-Me-4-ClPh	H	H	bond	486
133	Me	8-i-PrO	H	2-thienyl	H	H	bond	457
134	Me	8-i-PrO	H	3-thienyl	H	H	bond	457

Table 1 (continued)

Example	R^1	R^2	R^3	R^4	R^5	R^6	Z	MH^+
135	Me	8-i-PrO	H	3-furanyl	H	H	bond	441
136	Me	8-i-PrO	H	4-FPh	H	H	bond	469
137	Me	8-i-PrO	H	4-MeOPh	H	H	bond	481
138	Me	8-i-PrO	H	4-CF_3OPh	H	H	bond	535
139	Me	8-i-PrO	H	2-Me-4-ClPh	H	H	bond	500
140	Me	8-i-PrO	H	3-Me-4-ClPh	H	H	bond	500
141	Me	8-MeO	H	4-ClPh	2-F	H	bond	475
142	Me	8-Br	H	4-ClPh	2-F	H	bond	524
143	Me	8-MeO	H	4-ClPh	3-F	H	bond	475
144	Me	8-MeO	H	4-ClPh	3-CF_3	H	bond	525
145	H	H	i-Pr	4-ClPh	H	H	bond	455
146	Me	H	i-Pr	4-ClPh	H	H	bond	469
147	H	H	Me	3-thienyl	H	H	bond	399
148	Me	H	Me	3-thienyl	H	H	bond	413
149	H	H	Me	4-CNPh	H	H	bond	418
150	Me	H	Me	4-CNPh	H	H		
151	H	8-MeO	i-Pr	4-ClPh	H	H		
152	Me	8-MeO	i-Pr	4-ClPh	H	H		
153	H	8-MeO	Me	4-ClPh	H	H		
154	Me	8-MeO	Me	4-ClPh	H	H	bond	471429
175	Me	8-MeO	H	5-Me-2-thienyl	H	H	bond	479
176	Me	8-Br	H	5-Me-2-thienyl	H	H	bond	49
177	Me	8-Br	H	3,5-dimethylisoxazol-4-yl	H	H	bond	49
178	Me	8-Br	Pr	3,5-dimethylisoxazol-4-yl	H	H	bond	533
179	Me	8-Cl	H	3,5-dimethylisoxazol-4-yl	H	H	bond	446
180	Me	8-Cl	Pr	3,5-dimethylisoxazol-4-yl	H	H	bond	489
181	Me	8-H	H	5-Me-2-furyl	H	H	bond	397
182	Me	8-Br	H	5-Me-2-furyl	H	H	bond	476
183	Me	8-Cl	H	5-Me-2-furyl	H	H	bond	431
184	Me	8-MeO	H	5-Me-2-furyl	H	H	bond	427
185	Me	8-MeO	H	4-Me-2-thienyl	H	H	bond	443

Table 1 (continued)

Example	R^1	R^2	R^3	R^4	R^5	R^6	Z	MH^+
97	Me	8-MeO	H	4-CNPh	H	H	bond	448
98	H	8-MeO	H	4-(NMe_2)Ph	H	H	bond	452
99	Me	8-MeO	H	4-(NMe_2)Ph	H	H	bond	466
100	H	8-MeO	H	Ph	H	H	O	425
101	Me	8-MeO	H	Ph	H	H	O	439
102	H	8-MeO	H	4-ClPh	H	H	O	459
103	Me	8-MeO	H	4-ClPh	H	H	O	473
104	H	8-MeO	H	2-thienyl	H	H	bond	415
105	Me	8-MeO	H	2-thienyl	H	H	bond	429
106	H	8-MeO	H	5-Cl-2-thienyl	H	H	bond	449
107	Me	8-MeO	H	5-Cl-2-thienyl	H	H	bond	463
108	H	8-MeO	H	3-thienyl	H	H	bond	415
109	Me	8-MeO	H	3-thienyl	H	H	bond	429
110	H	8-MeO	H	3-furanyl	H	H	bond	399
111	Me	8-MeO	H	3-furanyl	H	H	bond	413
112	H	8-MeO	H	4-pyridyl	H	H	bond	410
113	Me	8-MeO	H	4-pyridyl	H	H	bond	424
114	H	H	H	4-ClPh	3-F	H	bond	431
115	Me	H	H	4-ClPh	3-F	H	bond	445
116	H	H	H	4-ClPh	3-Cl	H	bond	416
117	H	8-EtO	H	4-ClPh	H	H	bond	457
118	Me	8-EtO	H	4-ClPh	H	H	bond	471
119	H	8-i-PrO	H	4-ClPh	H	H	bond	471
120	Me	8-i-PrO	H	4-ClPh	H	H	bond	485
121	H	8-EtO	H	4-ClPh	3-Me	H	bond	472
122	Me	8-EtO	H	4-ClPh	3-Me	H	bond	486
123	H	8-i-PrO	H	4-ClPh	3-Me	H	bond	486
124	Me	8-i-PrO	H	4-ClPh	3-Me	H	bond	500
125	H	8-i-PrO	H	2-thienyl	H	H	bond	443
126	H	8-i-PrO	H	3-thienyl	H	H	bond	443
127	H	8-i-PrO	H	3-furanyl	H	H	bond	427
128	H	8-i-PrO	H	4-FPh	H	H	bond	455
129	H	8-i-PrO	H	4-MeOPh	H	H	bond	467
130	H	8-i-PrO	H	4-CF_3OPh	H	H	bond	521
131	H	8-i-PrO	H	2-Me-4-ClPh	H	H	bond	486
132	H	8-i-PrO	H	3-Me-4-ClPh	H	H	bond	486
133	Me	8-i-PrO	H	2-thienyl	H	H	bond	457
134	Me	8-i-PrO	H	3-thienyl	H	H	bond	457

All of the compounds listed below in Table 2 relate to compounds of the formula (IF):

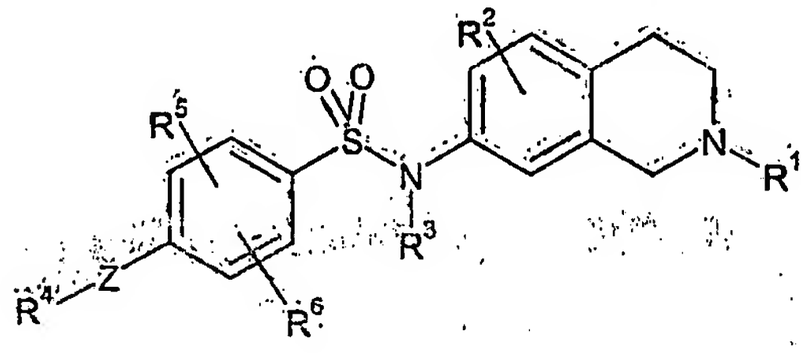


Table 2

Example	R^1	R^2	R^3	R^4	R^5	R^6	Z	MH^+
8	H	H	H	4-ClPh	H	H	bond	399
48	Me	H	H	4-ClPh	H	H	bond	413
49	Me	H	H	2-ClPh	H	H	bond	413
50	H	H	H	3-ClPh	H	H	bond	399
51	Me	H	H	3-ClPh	H	H	bond	413
52	Me	H	H	3,4-diClPh	H	H	bond	447
53	Me	H	H	2,4-diClPh	H	H	bond	447
54	H	H	H	4-BrPh	H	H	bond	444
55	Me	H	H	4-BrPh	H	H	bond	458
56	Me	H	H	4-FPh	H	H	bond	393
57	H	H	H	3-MePh	H	H	bond	379
58	Me	H	H	3-MePh	H	H	bond	393
59	H	H	H	4-CF_3Ph	H	H	bond	433
60	H	H	H	4-OCF_3Ph	H	H	bond	449
61	Me	H	H	4-OCF_3Ph	H	H	bond	463
62	H	H	H	4-t-BuPh	H	H	bond	421
63	Me	H	H	4-t-BuPh	H	H	bond	435
64	H	H	H	5-Cl-2-thienyl	H	H	bond	405
65	Me	H	H	5-Cl-2-thienyl	H	H	bond	419
66	H	H	H	2-naphthyl	H	H	bond	415
67	Me	H	H	2-naphthyl	H	H	bond	429
68	H	H	Me	4-ClPh	H	H	bond	413
69	Me	H	Me	4-ClPh	H	H	bond	427
70	H	H	H	4-ClPh	3-Me	H	bond	413
71	Me	H	H	4-ClPh	3-Me	H	bond	427
72	H	6-MeO	H	4-ClPh	H	H	bond	429
73	H	6-MeO	H	4-ClPh	3-Me	H	bond	443
155	H	6-MeO	H	3-ClPh	H	H	bond	429
156	H	6-MeO	H	2,4-diClPh	H	H	bond	464
157	H	6-MeO	H	2-Me-4-ClPh	H	H	bond	443
158	H	6-MeO	H	4-MeOPh	H	H	bond	425

Table 2 (continued)

Example	R^1	R^2	R^3	R^4	R^5	R^6	Z	MH^+
159	H	6-MeO	H	4-CNPh	H	H	bond	420
160	H	6-MeO	H	PhO	H	H	O	411
161	H	6-MeO	H	4-ClPhO	H	H	O	445
162	H	6-MeO	H	2-thienyl	H	H	bond	401
163	H	6-MeO	H	3-thienyl	H	H	bond	401
164	H	6-MeO	H	3-furanyl	H	H	bond	385
165	H	6-MeO	H	4-pyridyl	H	H	bond	396
166	H	H	H	4-ClPh	3-F	H	bond	417

5

All of the compounds listed below in Table 3 relate to compounds of formula (IE):

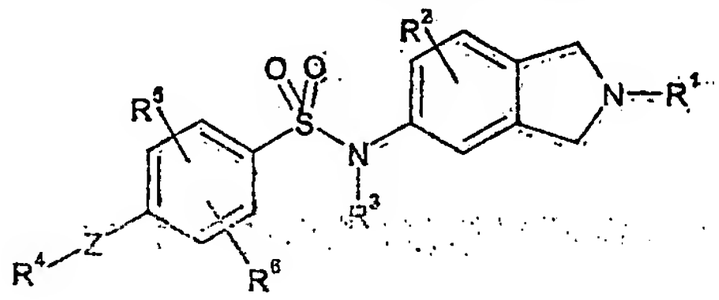


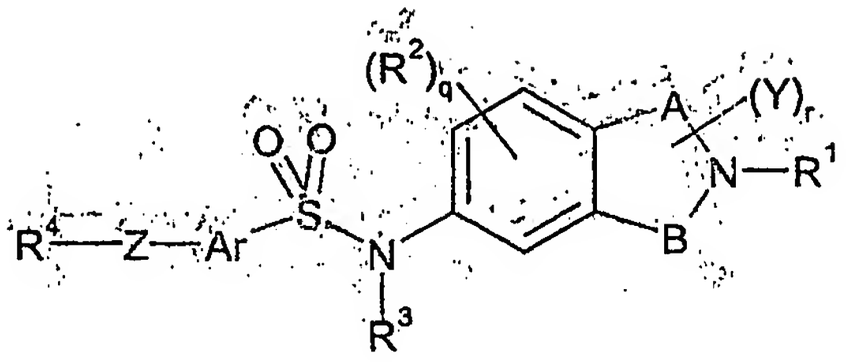
Table 3

Example	R^1	R^2	R^3	R^4	R^5	R^6	Z	MH^+
9	H	H	H	4-ClPh	H	H	bond	385
10	Me	H	H	4-ClPh	H	H	bond	399
167	H	H	H	4-ClPh	3-Me	H	bond	399
168	Me	H	H	4-ClPh	3-Me	H	bond	413
169	H	H	H	4-ClPh	3-F	H	bond	403
170	Me	H	H	4-ClPh	3-F	H	bond	417
171	H	H	H	4-ClPh	3-CF_3	H	bond	453
172	H	H	H	4-ClPh	3-MeO	H	bond	415
173	Me	H	H	4-ClPh	3-MeO	H	bond	429
174	Me	H	H	4-ClPh	3-CF_3	H	bond	467

10

Claims

1. A compound of formula (I)



(I)

wherein

A and B represent the groups $-(CH_2)_m-$ and $-(CH_2)_n-$ respectively;

R^1 represents hydrogen or C_{1-6}alkyl;

R^2 represents hydrogen, halogen, hydroxy, cyano, nitro, hydroxyC_{1-6}alkyl, trifluoromethyl, trifluoromethoxy, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{3-7}cycloalkylC_{1-6}alkoxy, $-(CH_2)_pC_{3-6}$cycloalkyl, $-(CH_2)_pC_{3-6}$cycloalkyloxy, $-COC_{1-6}$alkyl, $-SO_2C_{1-6}$alkyl, $-SOC_{1-6}$alkyl, $-S-C_{1-6}$alkyl, C_{1-6}alkylsulfonyloxy, C_{1-6}alkylsulfonylC_{1-6}alkyl, $-CO_2C_{1-6}$alkyl, $-CO_2NR^7R^8$, $-SO_2NR^7R^8$, C_{1-6}alkylsulfonamido, C_{1-6}alkylsulfonamidoC_{1-6}alkyl, $-(CH_2)_pNR^7R^8$, C_{1-6}alkylamidoC_{1-6}alkyl, $-(CH_2)_pNR^7COR^8$, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6}alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-6}alkyl, arylcarboxamidoC_{1-6}alkyl, aroyl, aroylC_{1-6}alkyl, arylC_{1-6}alkanoyl, $-SO_2NR^7R^8$, optionally substituted [illegible] substituted heteroaryl or optionally substituted heterocyclyl, or [illegible] $SO_2NR^7R^8$ wherein R^7 and R^8 together may be fused to form a 5- [illegible]-membered non-aromatic heterocyclic ring optionally interrupted by an O or S atom;

R^3 represents hydrogen or C_{1-6}alkyl;

Ar represents optionally substituted phenyl or optionally substituted monocyclic heteroaryl group;

R^4 represents optionally substituted aryl or optionally substituted heteroaryl;

R^7 and R^8 each independently represent hydrogen, C_{1-6}alkyl or together form a [illegible]-membered heterocyclic ring;

Z represents a bond, an oxygen atom or C_{1-6}alkyl;

Y represents hydrogen or C_{1-6}alkyl;

m and n independently represent an integer selected from 1 and 2;

p independently represents an integer selected from 0, 1, 2 and 3;

q represents an integer from 1 to 3;

r represents an integer from 1 to 4;

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound of formula (I) which is

4-(4-Chloro-phenyl)-*N*-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide;

4-(4-Chloro-phenyl)-*N*-(3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide;

4-(4-Chloro-phenyl)-*N*-methyl-*N*-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide;

4-(4-Chloro-phenyl)-*N*-methyl-*N*-(3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide;
4-(3,4-Dichloro-phenyl)-*N*-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide hydrochloride;
4-(4-Chloro-phenyl)-*N*-(8-methoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide hydrochloride;
4-(4-Chloro-phenyl)-*N*-(8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide hydrochloride;
4-(4-Chloro-phenyl)-*N*-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-benzenesulfonamide;
4-(4-Chloro-phenyl)-*N*-(2,3-dihydro-1*H*-isoindol-5-yl)-benzenesulfonamide hydrochloride;
4-(4-Chloro-phenyl)-*N*-(2-methyl-2,3-dihydro-1*H*-isoindol-5-yl)-benzenesulfonamide;
4-(4-Chloro-phenyl)-3-methyl-*N*-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide hydrochloride;
4-(4-Chloro-phenyl)-3-methyl-*N*-(3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide;
4-(4-Chloro-phenyl)-3-methyl-*N*-(8-methoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide hydrochloride;
4-(4-Chloro-phenyl)-3-methyl-*N*-(8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide;
4-(5-Chloro-thiophen-2-yl)-N-(8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-benzo[d]azepin-7-yl)-benzenesulfonamide;
4-(5-Chloro-thiophen-2-yl)-2-fluoro-N-(8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-benzo[d]azepin-7-yl)-benzenesulfonamide;
4-(4-Chloro-phenyl)-*N*-(8-dimethylamino-3-methyl-2,3,4,5-tetrahydro-1*H*-benzazepin-7-yl)-benzenesulfonamide hydrochloride and
4-(4-fluorobenzyl)-*N*-(3-methyl-2,3,4,5-tetrahydro-1*H*-benzo[d]azepin-7-yl)-benzenesulfonamide hydrochloride.

3. A pharmaceutical composition comprising a compound of formula (I) as claimed in claims 1 or 2 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor.

4. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in claims 1 or 2, for use in therapy.

5. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in claims 1 or 2 for use in a condition which requires modulation of a dopamine receptor.

6. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof according to claim 5 wherein the condition is selected from psychotic disorders, Parkinsons disease, substance abuse, dyskinetic disorders, depression, bipolar disorder, anxiety, cognitive impairment, eating disorders, obesity, sexual dysfunction, sleep disorders, emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, autism, vertigo, dementia, circadian rhythm disorders and gastric motility disorders.

7. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in claims 1 or 2 in the manufacture of a medicament for the treatment of a condition which requires modulation of a dopamine receptor.

8. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof according to claim 7 wherein the condition is selected from psychotic disorders, Parkinsons disease, substance abuse, dyskinetic disorders, depression, bipolar disorder, anxiety, cognitive impairment, eating disorders, obesity, sexual dysfunction, sleep disorders, emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, autism, vertigo, dementia, circadian rhythm disorders and gastric motility disorders.

9. A method of treating a condition which requires modulation of a dopamine receptor, which comprises administering to a mammal in need thereof an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in claims 1 or 2.

10. A method of treating a condition according to claim 9 wherein the condition is selected from psychotic disorders, Parkinsons disease, substance abuse, dyskinetic disorders, depression, bipolar disorder, anxiety, cognitive impairment, eating disorders, obesity, sexual dysfunction, sleep disorders, emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, autism, vertigo, dementia, circadian rhythm disorders and gastric motility disorders.

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D223/16 C07D409/10 C07D407/10 C07D401/10 C07D413/10
C07D403/10 C07D217/04 C07D209/44 A61K31/40 A61K31/47
A61K31/55 A61P3/04 A61P25/30 A61P25/24 A61P25/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 02502 A (MOSS STEPHEN FREDERIK ;BROMIDGE STEVEN MARK (GB); SMITHKLINE BEECH) 21 January 1999 (1999-01-21) cited in the application claims 1,4,10	1-10
A	WO 01 32646 A (BROMIDGE STEVEN MARK ;SERAFINOWSKA HALINA TERESA (GB); SMITHKLINE) 10 May 2001 (2001-05-10) cited in the application claims 1,5,9	1-10
A	WO 98 27081 A (BROMIDGE STEVEN MARK ;KING FRANCIS DAVID (GB); SMITHKLINE BEECHAM) 25 June 1998 (1998-06-25) cited in the application claims 1,13,14	1-10

[ ] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 May 2003	16/05/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schuemacher, A

Form PCT/ISA/210 (second sheet) (July 1992)

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P25/20 A61P25/18 A61P25/14 A61P25/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 May 2003	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Schuemacher, A

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 9 and 10 are directed to a method of treatment of the human/animal body; the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9902502 A	21-01-1999	AU 736256 B2	26-07-2001
		AU 9257898 A	08-02-1999
		BR 9810991 A	08-08-2000
		CN 1087294 B	10-07-2002
		CN 1261883 T	02-08-2000
		WO 9902502 A2	21-01-1999
		EP 0994862 A2	26-04-2000
		HU 0003073 A2	29-01-2001
		JP 2002511097 T	09-04-2002
		NO 20000108 A	10-01-2000
		NZ 501258 A	27-07-2001
		PL 338016 A1	25-09-2000
		TR 200000073 T2	21-06-2000
		TW 470743 B	01-01-2002
		US 6316450 B1	13-11-2001
		ZA 9806139 A	10-01-2000
WO 0132646 A	10-05-2001	AU 1278701 A	14-05-2001
		WO 0132646 A2	10-05-2001
		EP 1228066 A2	07-08-2002
WO 9827081 A	25-06-1998	AU 729056 B2	25-01-2001
		AU 6090498 A	15-07-1998
		BG 103530 A	31-01-2000
		BR 9713734 A	28-03-2000
		CN 1246116 A	01-03-2000
		CZ 9902203 [illegible]	17-[illegible]
		EA 2351 [illegible]	25-[illegible]
		WO 9827081 [illegible]	25-06-[illegible]
		EP 0946539 A1	06-10-[illegible]
		HU 0000658 A2	28-02-[illegible]
		JP 2001506646 T	22-05-2001
		NO 993003 A	18-06-1999
		NZ 335970 A	26-[illegible]-20[illegible]
		PL 334337 A1	28-02-20[illegible]
		SK 80899 A3	14-02-20[illegible]
		TR 9901361 T2	23-08-19[illegible]
		TW 418205 B	11-01-2001
		US 6423717 B1	23-07-2002
		ZA 9711319 A	17-06-1999